PROSPERITAS VESTRA FINIS NOSTRA!

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DETERMINANTS OF QUALITY OF LIFE IN PATIENTS WITH NONRADIOGRAPHIC AXIAL SPONDYLOARTHRITIS: ANALYSIS BASED ON MAIN ASPECTS OF THE DISEASE.

THESIS SUMMARY

OF DISSERTATION WORK FOR AWARDING THE EDUCATIONAL AND SCIENTIFIC DEGREE "DOCTOR"

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The doctoral student works as a doctor specializing in Rheumatology at the Clinic of Rheumatology at the University Multidisciplinary Hospital for Active Treatment "St. Marina », Varna and is an assistant at the Department of Internal Medicine, Department of Rheumatology, Medical University - Varna. The clinical trials were performed in the Clinic of Rheumatology of the University Hospital "St. Marina »- Varna.

The dissertation was discussed and directed for public presentation at a meeting of the Department of Propaedeutics of Internal Medicine, MU - Varna.

The dissertation contains 158 typewritten pages and is illustrated with 35 figures, 40 tables and 14 appendices. The list of cited literature includes 202 titles, of which 1 in Cyrillic and 201 in Latin.

Note: The numbers of the tables and figures in the thesis summary do not correspond to those in the dissertation.

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The public presentation of the dissertation will take place on 21.07.2022 at 12:00 in the Medical University "Prof. Dr. Paraskev Stoyanov "- Varna at an open meeting of the scientific :ury.

The materials on the dissertation are published on the website of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna and are available at the Department of Propaedeutics of Internal Medicine at MU - Varna.

CONTENTS

ABBREVIATIONS

ANKH gene	A gene encoding a protein that affects skeletal formation
anti-TNF	Anti-tumor necrosis factor
ASAS	Assesment in SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score, calculated with CRP
ASQoL	Ankylosing Spondylitis Quality of Life
ax SpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BME	Bone marrow oedema
CRP	C-reactive protein
DFI	Dougados Functional Index
EQ-5D	Euro Quality of Life
EULAR	Europenian League against rheumatism
FM	Fat metaplasia
HAQ	Health Assessment Questionnaire
HLA B27	Human leukocyte antigen B27
HRQoL	Health-related quality of life
IBD	Inflammatory bowel disease
IBP	Inflammatory back pain
IL-17a	Interleukine – 17 a
IL-18	Interleukine - 18
IL-6	Interleukine н – 6
JSN	Joint space narrowing
MASES	Maastrich Ankylosing Spondylitis Enthesitis Score
MCS	Mental Composite Score
mSASSS	Modified Stoke Ankylosing Spondylitis Spinal Score
nr-ax SpA	Nonradiographic axial spondyloarthritis
NYHA	New York Heart Association
OMERACT	Outcome Measures in Rheumatology Clinical Trials
SPARCC	Spondyloarthritis Research Consortium of Canada scorring system
STIR	short-TI inversion recovery
VAS	Visual analogue scale
TNAP	Tissue nonspecific alkaline phosphatase

I. INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that mainly affects the sacroiliac joints and spine. This term includes the classic example of inflammatory joint disease - ankylosing spondylitis (AC), as well as the prevailing in recent years - radiographic axial spondyloarthritis (nr-axSpA). The absence of conclusive radiographic evidence of structural changes in the sacroiliac joints serves to distinguish AC from nr-axSpA. Both groups of patients are characterized by active inflammatory changes detected by magnetic resonance imaging (MRI) of sacroiliac joints, which with the progression of the disease are transformed into chronic structural changes.

The progress is largely due to the continuous work of international experts from the Assistance in SpondyloArthritis International Society (ACAS). Their initial developments focused on the early stages of axial spondyloarthritis, the development of criteria for inflammatory spinal pain, and the updating of the classification criteria for spondyloarthritis. The work of ASAS experts is the new concept, which deals with spondyloarthritis in two main forms - mostly peripheral or mostly axial. Attention is also paid to the evaluation of the response in the treatment of patients with arthritis, creation, validation and implementation in practice of a wide range of evaluation scores for monitoring disease activity, response to treatment, staging changes in imaging studies and more.

The main goal of the ASAS experts is to focus attention on the problems of patients with spondyloarthritis, making possible early diagnosis, adequate monitoring and evaluation of the effect of the individual therapeutic approach.

Quality of life is impaired in all rheumatic diseases. A study by ***Salaffi F. et al***. from 2019 compares the quality of life in 2633 patients with various rheumatic diseases and summarizes that it is the worst in the group of patients with inflammatory joint disease. Dominant effects on the physical function of participants have been reported to be predominant over other aspects of quality of life. *(Salaffi F. et al., 2109)*

The introduction and application in everyday practice of the ASAS criteria have contributed to the possibility of early diagnosis of patients in the pre-radiographic phase of spondyloarthritis. This early detection of the disease inevitably led to an increased number of patients worldwide and the associated social and economic consequences (*Landewe R. et al, 2015).*

The impact of axial spondyloarthritis on quality of life is even more significant, given the fact that symptoms of the disease by definition start before the 45th anniversary (Rudwaleit et al., 2011). In the active age stage of the patient, chronically progressive inflammatory joint disease significantly limits various aspects of daily activities (*Braun J. et al., 2011), (van Lunteren et al., 2018), (Singh J. et al., 2009).*

Axial SpA impairs health-related quality of life (HRQoL) *(Singh J. et al., 2009)*. Several studies comparing health-related quality of life in patients with axial spondyloarthritis and the general population have reported a statistically significantly lower HRQoL in patients with spondyloarthritis *(Braun J. et al., 2011), (Singh J. et al., 2009).* In the context of axial spondyloarthritis, the decrease in HRQoL is more significant at the expense of changes in the physical function of patients compared to the psycho-emotional aspects of the disease *(Dagfinrud et al., 2004), (Davis et al., 2005).*

The effect of the disease on the physical function of patients is significant. It is also reflected in a number of other aspects of life - in personal and social terms (education, starting a family and career growth). Separate scientific publications have analyzed the impact of the overall level of disease activity in patients with spondyloarthritis and employment and productivity *(Boonen et al., 2006; Haglund et al., 2013; Healey et al., 2011*).

The expansion of the range of therapeutic agents from the group of anticytokine therapy in spondyloarthritis coincides with the development of the ASAS criteria and again shifts the focus to the problem of quality of life of patients with nr- / r-ax SpA (*Jasvinder et al., 2009*).

It has been found that a number of factors are associated with difficulties at work and loss of productivity in the workplace (*Boonen et al., 2006, Dimitrov et al. 2013*). Unemployment is associated with older patients, social deprivation, long-term illness, functional impairment and depression. Absenteeism is associated with disease activity and depression, while presenteeism is associated with older patients, disease activity, anxiety, and the level of depression. *(Healey et al., 2011; Dimitrov et al. 2013).*

Patients with nr-ax SpA have a shorter duration of symptoms of the disease and although there are no radiological signs, they are characterized by a significant severity of the disease *(Ivanova M. et al., 2018*). Compared with patients with r-axSpA, the levels of disease activity assessed by the patient and the functional changes associated with the disease show similar results (*Gracey et al., 2016*).

Analyzes of the two phases of ax SpA - nr-ax SpA and ax SpA, indicate differences related to the duration of symptoms, gender distribution and age of patients. Despite the significantly lower degree of inflammatory activity, as well as relatively preserved axial mobility in patients with nr-ax SpA, the two phases have similarities in terms of disease activity, physical function and quality of life (*Ivanova M. et al., 2018 , Boonen et al., 2015).*

The DESIR study monitored the quality of life in patients up to 50 years of age with evidence of early inflammatory spinal pain for up to 8 years. A link has been established between ASDAS calculated by CRP and quality of life due to physical function. The same study did not prove a link between quality of life and MCS (Mental composite score). The level of disease activity partly contributes to the deteriorating quality of life, and according to the authors there are other factors that change it *(Puyraimond-Zemmour et al., 2019).*

A number of scientific studies have revealed the indirect negative impact of smoking on the quality of life in patients with nr-ax SpA, as well as its later phase (*Akar et al., 2018, Zhao et al., 2017, Deminger et al., 2018).* It is mainly due to the relationship between it and the likelihood of progression of structural changes in the SIS and the spine. ***Ho Yin Chung et al***. in 2016 prove that smoking is an independent factor associated with the overall level of disease activity, structural damage, motor deficit and resp. quality of life. Deteriorated quality of life was observed by the authors in both sexes with nr-ax SpA (*Tsang et al., 2019).*

Different scales for assessing the level of quality of life in patients with axial spondyloarthritis have been used in the literature. Patient-reported data are categorized into two main groups of quality of life assessment tools - generic and specific (Ankylosing Spondylitis Quality of Life - ASQoL) (*Wells et al., 2011)*. The disease-specific quality of life questionnaire ASQoL has been widely used in a wide range of spondyloarthritis (*van Tubergen et al., 2015*). It is easy for the patient to perceive, involves aspects not only focused on the patient's physical function, and takes no more than 5 minutes to complete *(Doward et al., 2003*).

II. PURPOSE

The aim of the present study was to examine the quality of life and factors influencing it (including the main aspects of the disease - activity, function and disability measured by patient-reported results, spinal mobility and SIJs status on MRI) in patients with nr-ax SpA from the Bulgarian population.

III. TASKS:

1. To assess the severity of symptoms by measuring the level of disease activity in patients with nr-ax SpA, including extraaxial manifestations given the heterogeneous phenotypic manifestation of the disease.

2. To assess the degree of inflammation of the sacroiliac joints (SIS), using the magnetic resonance scoring system for SPARCC activity and to investigate the association between indicators of clinical disease activity and inflammation of magnetic resonance imaging (MRI).

3. To investigate the extent to which the disease creates limitations in physical function through a comparative analysis of patients with nr-ax SpA and healthy individuals.

4. To analyze the changes in the spinal mobility and the status of the musculoskeletal system as a whole (including involvement of peripheral joints, entheses, dactylitis) in the Bulgarian population of patients with nr-ax SpA.

5. To study the health-related quality of life and the risk factors for its deterioration.

6. To investigate the clinical, laboratory and MRI characteristics in men and women and to determine whether there are gender differences in the severity of nr-ax SpA.

7. To study the connection of the individual pharmacological therapies with the clinical and laboratory parameters of the disease process.

IV. MATHERIAL AND METHODS

IV.1 Design and distribution of research participants

All participants in the research were invited to participate in it, and they were explained the details of the individual steps. Their participation continued after the voluntary signing of informed consents (for inclusion in the research, for hospitalization and conducting research on the relevant algorithms and for conducting magnetic resonance imaging of sacroiliac joints). All patients have passed through the Rheumatology Clinic of UMHAT "St. Marina" - EAD - Varna, aimed at proving or excluding nr-ax SpA by general practitioners, rheumatologists and specialists from other specialties close to rheumatology. A number of events and campaigns of the research team to clarify the early and specific symptoms of the disease among colleagues in the districts of Varna, Burgas and Ruse also benefited from the focused thinking for nr-ax SpA.

All participants were screened and assigned based on the ASAS questionnaire to prove or exclude inflammatory spinal pain. After conducting all the studies, three groups were formed - patients with nr-ax SpA - shaped arm, nr-ax SpA - clinical arm and a control group of patients with non-inflammatory type of pain in the spine (Figure 1). We used the following inclusion and exclusion criteria:

IV.2 Inclusion and exclusion criteria:

IV.2.1 Inclusion criteria:

1. Age of patients from 18 to 45.

2. Symptom duration not more than 3 years.

3. At least 4 of the 5 criteria for inflammatory back and back pain according to the ASAS criteria for IBP are available *(Sieper J. et al., 2009).*

4. Normal radiography of sacroiliac joints.

5. Lack of contraindications for magnetic resonance imaging (claustrophobia, pacemaker, implanted material incompatible with the MRT).

6. Signed informed consent of the patient to participate in the study, as well as a separate informed consent to conduct blood tests and magnetic resonance imaging of sacroiliac joints.

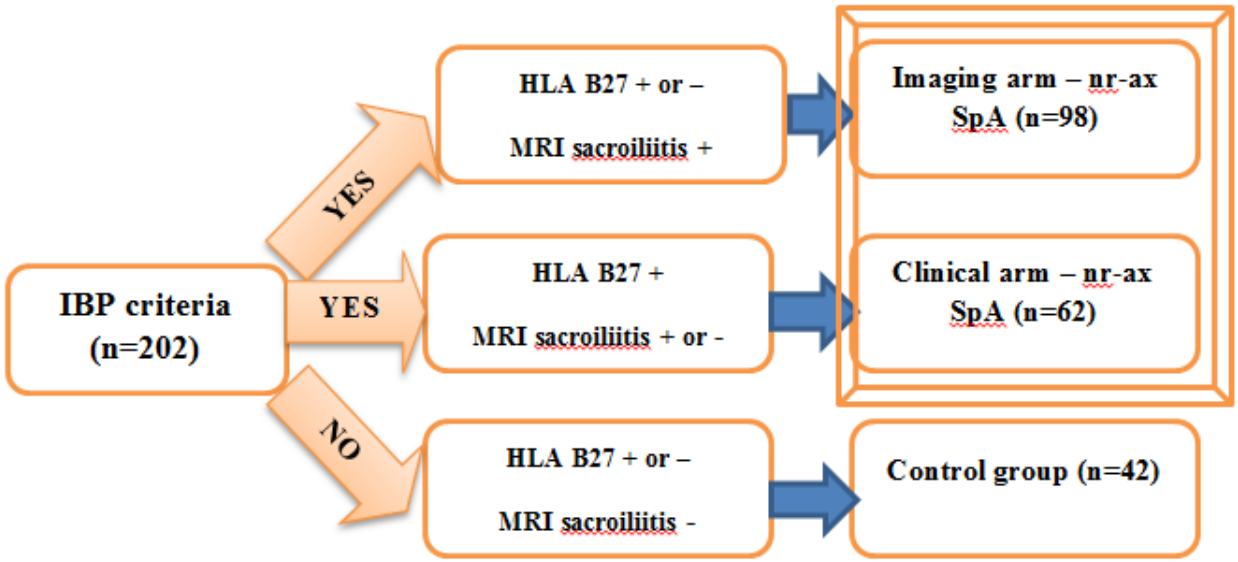
7. Patients treated with different treatment regimens:

- no treatment
- NSAIDs
- Sulfasalazine (up to 2000mg/d)

IV.2.2 Exclusion criteria

1. Symptom duration more than 3 years.
2. History or current neoplastic disease for the last 5 years.
3. History or concomitant lymphoproliferative disease.
4. History and accompanying documentation for significant comorbidity, incl. congestive heart failure II-IV functional class according to NYHA, active liver disease, severe renal failure, diabetes mellitus with poor control and complications.
5. Presence of previous conventional radiography of sacroiliac joints with data for sacroiliitis I-IV X-ray stage.
6. Available contraindications for magnetic resonance imaging (claustrophobia, implanted pacemaker, implanted material incompatible with the study).
7. Cognitive impairment, psychiatric illness or severe progressive or uncontrolled somatic illness that would affect participation in the study.
8. Patients treated with a biological agent (anti TNF alpha or IL-17A inhibitors).
9. Patients with available criteria for another rheumatic disease.

Figure 1: *Scheme of the design and distribution of the participants in the research:*



In the conditions of a cross-sectional study, data were collected on:

- Age of the patients
- Gender
- Symptom duration
- HLA B27 antigen
- Smoking status
- Presence of concomitant diseases
- Information about treatment
- Results of laboratory markers for inflammation – ESR and CRP
- The results of the completed clinical disease-specific scores for determining the disease activity - BASDAI, ASDAS, calculated with CRP, total VAS assessment according to the patient and the doctor
- Results of the completed questionnaire for assessment of the functional status of patients – BASFI
- Results of the physical examination of the musculoskeletal system and determination of the degree of limitations in spinal mobility using the BASMI questionnaire

- Results of the completed questionnaire for assessment of quality of life in spondyloarthritis – ASQoL

- Results of reading the MRI of the SIJs and determining the SPARCC and SPARCC minus

- The presence of changes in the MRI of the SIJs due to a previous acute inflammatory process - erosions, narrowing of the joint space and fat metaplasia.

- The presence of extraaxial symptoms in the context of SpA - peripheral arthritis, enthesitis, dactylitis, uveitis and psoriasis.

IV.3 Methods for certifying the disease activity applied in the scientific research

IV.3.1 Detailed anamnesis - collected information on demographic factors, age and specific characteristics of symptoms, family history, etc.

IV.3.2 Detailed physical examination, including musculoskeletal status:

IV.3.2.1 Assessment of the degree of damage to the axial skeleton:

We used the composite index for assessing spinal mobility - **Bath Ankylosing Spondylitis Merology Index - BASMI**. It includes 5 aspects of physical examination, which cover the ranges of movement and restrictions in them in the cervical and lumbar segments of the spine and hips. The possibility of performing dorsal flexion in the cervical spine (tragus - wall distance), cervical rotation, flexion in the lumbar region, lateral flexion in the lumbar region and intermaleolar distance in cm is assessed. The limitation in the latter is an early screening scar for involvement of the hip joints and extraarticular soft tissues in the area. Results range from 0 to 10, with 0 indicating a lack of motor deficit and 10 indicating severe limitations in spinal mobility (*Feldkeller et al., 1998*).

IV.3.2.2 Examination of peripheral joints, entheses, dactylitis

IV.3.2.3 Detection of ocular symptoms (uveitis) or skin rash (psoriasis)

IV.3.2.4 Physical status of other organs and systems

IV3.3 Clinical indices for assessment of disease activity:

IV.3.3.1. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questionnaire is recommended by the ASAS and is used daily in clinical practice to determine the degree of disease activity as well as to respond to treatment. BASDAI consists of 6 questions on the method of visual analog scale (from 0 to 10 cm) and is

entirely based on the results reported by the patient. It is generally accepted that disease activity is determined to be high at BASDAI values ≥4. In the case of BASDAI ≤4 are considered inactive disease at the time *(Marona et al., 2020).*

IV.3.3.2 Assessment of disease activity according to the **Ankylosing Spondylitis Disease Activity Score - ASDAS.** Compared to BASDAI, ASDAS consists of patient-reported data on - stiffness, back pain, general assessment, pain / swelling in peripheral joints, but biomarkers for laboratory activity - acute phase parameters - ESR and CRP *(Chimenti et al., 2020).* In the present scientific paper we used only CRP for calculation of ASDAS. The formula for ASDAS - CRP is as follows: ASDAS- CRP = 0.12 x back pain + 0.06 x duration of morning stiffness + 0.11 x overall patient score + 0.07 x peripheral joint pain / swelling + 0.58 x Ln (CRP + 1). As is generally accepted, we formed 4 categories of disease activity according to the values of ASDAS-CRP: <1.3 inactive disease, 1.3-2.1 - moderate degree of activity, 2.1-3.5 - high degree of activity and over 3.5 - very high degree of disease activity.

IV.3.3.3 Assessment of disease activity by - **Overall assessment of VAS** disease activity by the patient and the physician (*van Tubergen et al., 2002*). A horizontal line with a length of 0.0 to 10 cm is used, with two values - 0 and 10 at both ends. VAS is valid and reliable in the study of subjective experiences such as pain. It is filled in twice - once by the patient, taking into account the disease activity of his own suffering and once by the attending physician during the examination. A score of 0.0 indicates inactive disease and 10 indicates a very high degree of disease activity.

IV.3.4. Assessment of the physical function of patients:

IV.3.4.1 The assessment of physical function was performed using **the Bath Ankylosing Spondylitis Funcional Index - BASFI.** This test has been recommended by the ASAS to determine the degree of functional impairment in SpA (*Maksymovich et al., 2007*). The questionnaire consists of 8 questions by the method of visual analog scale (each with a score from 0.0 to 10). Six of the questions are related to specific movements in a particular joint area, and the other two are general and relate to the overall functioning of the musculoskeletal system in everyday activities. The result of BASFI is a score from 0.0 to 10.0 and is composed of the arithmetic mean of the values of the answers to the eight questions.

IV.3.5 Assessment of quality of life in non-radiographic axial spondyloarthritis

IV.3.5.1 To assess the level of quality of life in patients with non-radiographic axial spondyloarthritis, we used the **questionnaire Ankylosing Spondylits Quality of Life (ASQoL).** It is validated in patients with ankylosing spondylitis and is widely used in the medical literature in patients in the early phase - nr-ax SpA. It consists of 18 statements, each of which is given a positive - 1 point or a negative answer - 0 points. ASQoL scores can range from 0.0 (very good quality of life) to 18 (very poor quality of life). ASQoL is suitable for use in daily practice to monitor the status and dynamics of the disease in individual patients (*Doward et al., 2003).*

IV.3.6 Assessment of inflammation of the sacroiliac joints using the magnetic resonance scoring system SPARCC and SPARCC minus:

IV.3.6.1 The most commonly used in the literature is **the Spondyloarthritis Research Consortium of Canada (SPARCC)**. It is formed after evaluation of MRI images of the sacroiliac joints, which are usually T1-weighted images and short-tau inversion recovery (STIR) technique with bone marrow suppression *(Baraliakos et al., 2005*). All indicators are dichotomous - the presence of bone marrow edema is indicated by 1, its absence by 0, and only 6 sections of the coronary projection are evaluated - most often from the 4th to the 9th. Each SIS is divided into 4 quadrants: 1 upper iliac, 2 lower iliac, 3 upper sacral, 4 lower sacral. The presence of an increased signal in each quadrant is recorded. The maximum score for the two SIS of each coronary section is 8. The maximum score for 6 coronary sections = 48. SPARCC, unlike SPARCC minus, also includes "intensity" and "depth" speed. The maximum score for "intensity" is 12, for "depth" - also 12. The total maximum score of SPARCC is 72.

IV.3.6.2 In parallel with the calculation of SPARCC, we evaluated the MRT index for the assessment of acute inflammatory changes of the SIJs - SPARCC minus *(Baraliakos et al., 2005, Landewe et al., 2005).* It is easier to calculate than SPARCC, because the "intensity" and "depth" scores are not involved in its formation. The maximum SPARCC minus score is 48.

IV.3.7 Investigation of laboratory markers of inflammation

IV.3.7.1 C-reactive protein (CRP) - was tested in the serum of patients by immunoturbidimetric methods of an automatic biochemical analyzer. We took 5 mg/l as the upper reference value of the normal.

IV.3.7.2 The erythrocyte sedimentation rate (ESR) was reported using automated technology. The manufacturing process includes work in a microcapillary, determining the aggregation capacity of the test sample and after performing mathematical models, the value of ESR in mm/h is electronically calculated. Like other studies in the medical literature, we accepted 28 mm/h as the upper limit of normal.

IV.4 Statistical methods used in the research:

IV.4.1 Descriptive statistics - through tables, graphs and summarizing numerical characteristics are described the main characteristics of the studied groups of patients and control group and the studied clinical and laboratory indicators.

IV.4.2 Statistical conclusions

IV.4.2.1 Statistical estimation **-** 95% confidence intervals are constructed, revealing the limits within which the attribute varies in the general population with 95% certainty.

IV.4.2.2. Test of statistical hypotheses at significance level $\alpha = 0.05$, which means that the conclusions drawn for the population on the basis of sample data are guaranteed with 95% certainty.

IV.4.2.2.1 parametric - test a statistical hypothesis for the difference between the averages of two independent samples.

IV.4.2.2.2 nonparametric - Chi-square ($\chi 2$) analysis of the independence of variables that are represented on weak scales.

IV.4.3 Regression and correlation analysis

V.4.3.1. Correlation analysis **-** used to determine the direction and strength of the relationship between two variables.

IV.4.3.1.1 Pearson's parametric correlation coefficient is used in cases where the relationship between the variables is linear.

IV.4.3.1.2 Non-parametric Spearman and Kendall correlation coefficients are used in cases where the relationship between the variables is nonlinear. The simultaneous use of the two coefficients serves to confirm the obtained results, as the non-parametric coefficients are more inaccurate.

IV.4.3.2. Regression analysis **-** used to model the relationship between one dependent and one (one-factor regression analysis) or more (multifactor regression analysis) independent variables.

The statistical analyzes in the dissertation were performed using the statistical product IBM SPSS v.26, and the graphic design of the dissertation via Microsoft Office (Excel) on Windows 10.

V. RESULTS

V.1 Distribution of participants in the research

V.1.1 General distribution:

In the current study, we included 202 patients with low back pain for more than 3 months. Of all patients, 160 had an inflammatory type of low back pain **(Appendix 12-III - ASAS criteria for IBP)**, while the remaining 42 patients had an insufficient number of criteria for inflammatory back pain and were assigned to a control group. The latter were accepted as patients with non-specific type of spinal pain, mostly of a mechanical nature, with no evidence of spondyloarthritis.

Following the application of the ASAS classification criteria for spondyloarthritis in 2010, participants in the group with inflammatory spinal pain were divided into two subgroups - **clinical and imaging arm** (respectively 62 patients with HLA B27 antigenic (+) + two or more manifestations of spondyloarthritis and 98 patients with MRI data for BME + at least one manifestation of spondyloarthritis).

Table 1: *Descriptive analysis of patients from different groups according to* ***gender, age, duration of symptoms, HLA B27 antigenic presence and intake of symptomatic*** or ***antirheumatic disease-modifying drugs:***

	Imaging arm Group A N = 98	**Clinical arm Group B N = 62**	**Conrol group Group C N = 42**
Gender: males %	51%	37%	45.2%

females %	49%	63%	54.8%
Age(years.) Mean ±SD	33.8±7.71	34.12±6.95	35.09±7.9
Symptom duration (years) Mean ±SD	0.76±0.26	0.48±0.13	1.17±0.33
Smokers: n (%) ***- non-smokers*** ***- smokers*** ***- ex-smokers >5y.***	 28 (28.6%) 60 (61.2%) 10 (10.2%)	 19(30.6%) 38 (61.3%) 5 (8.1%)	 28(66.7%) 10 (23.8%) 4 (9.5%)
HLA B27 antigenic presence, n (%)	79 (80.6%)	62 (100%)	6 (14.2%)
Treatment: n (%) - ***Without treatment*** - ***NSAIDs*** - ***Sulfasalazine 2g/d***	 35 (35.7%) 50 (51.1%) 13 (13.2%)	 24 (38.7%) 27 (43.6%) 11 (17.7%)	 28 (66.6%) 14 (34.4%) NA

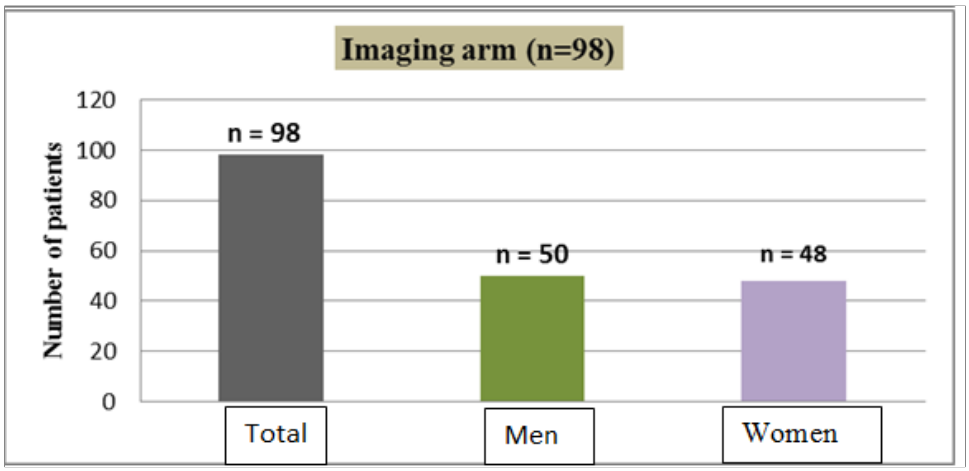
Legend*: NSAIDs - non-steroidal anti-inflammatory drugs, HLA B27 - human leucocyte antigen B27, mean ± SD - mean ± standard deviation.*

The antigenic presence of HLA B27 was observed in 80.6% of the patients in the imaging arm, in 100% of the patients in the clinical arm and in 14.6% of the control group. In subsequent analyzes, the subgroups of smokers and ex-smokers over 5 years of age will be merged.

The relative proportion of patients with nr-ax SpA who did not receive treatment was 36.8% compared to 66.6% of the control group. In the pooled group of patients (group A + group B), the number of patients taking non-steroidal anti-inflammatory drugs was 48.1% and that of sulfasalazine - 15%.

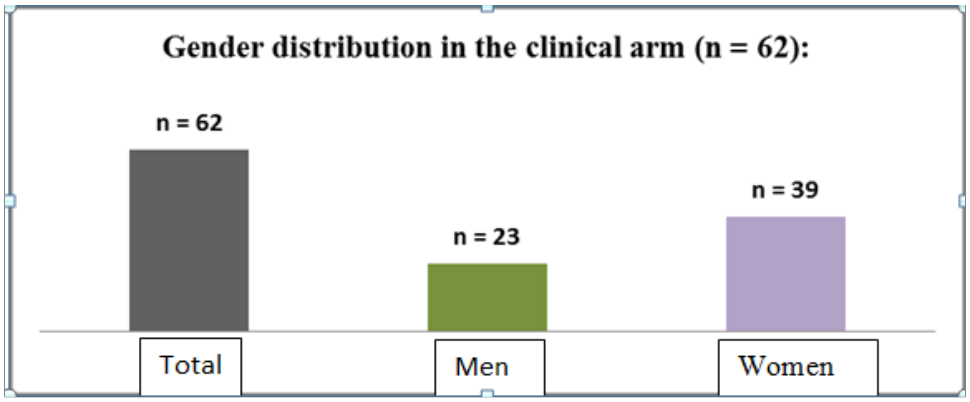
V.1.2 Distribution of patients by sex:

Figure 2: *Distribution by sex in the group of patients from the imaging arm:*



In the subgroup of nr-ax SpA patients, the relative proportion of men and women was approximately equal {51.02% (n = 50) versus 48.98% (n = 48), n = 98}.

Figure 3: *Gender distribution in the subgroup of patients from the clinical arm:*



The group of patients in **the clinical arm** is dominated by women - n = 39 (62.9%), compared to 23 (37.1%) men at n = 62. The generalized sex distribution in the whole group of patients with nr-ax SpA is presented in Figure 4, where the relative the share of **men** in the group of patients with nr-ax SpA was 45.6%, compared to 54.4% women. On Fig. 5, apart from subgroups, the distribution between the sexes is also presented for the participants included in the control group (45.2% men and 54.8% women, respectively):

Figure 4: *Gender distribution of all patients with* ***nr-ax SpA****:*

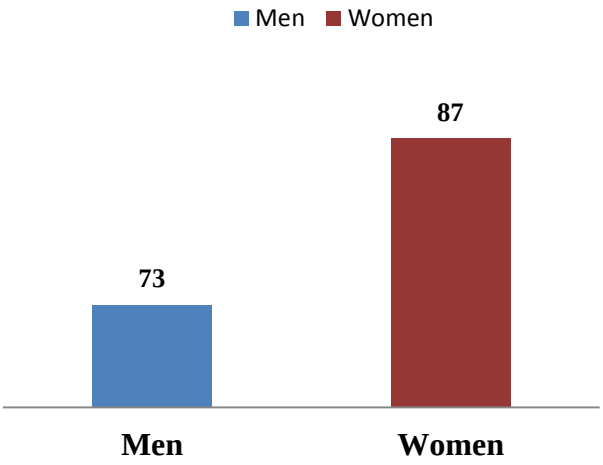
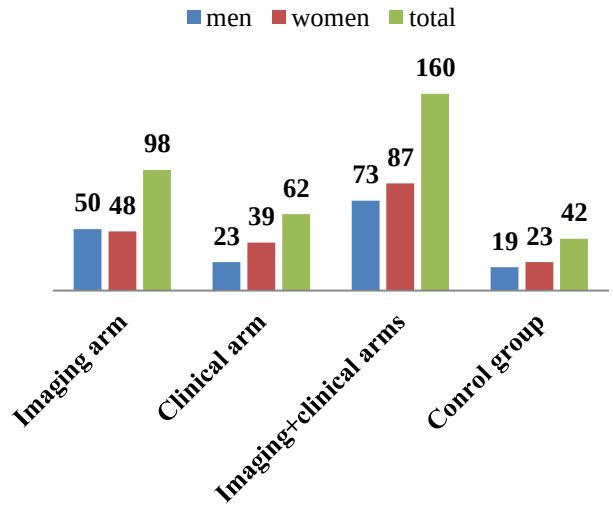
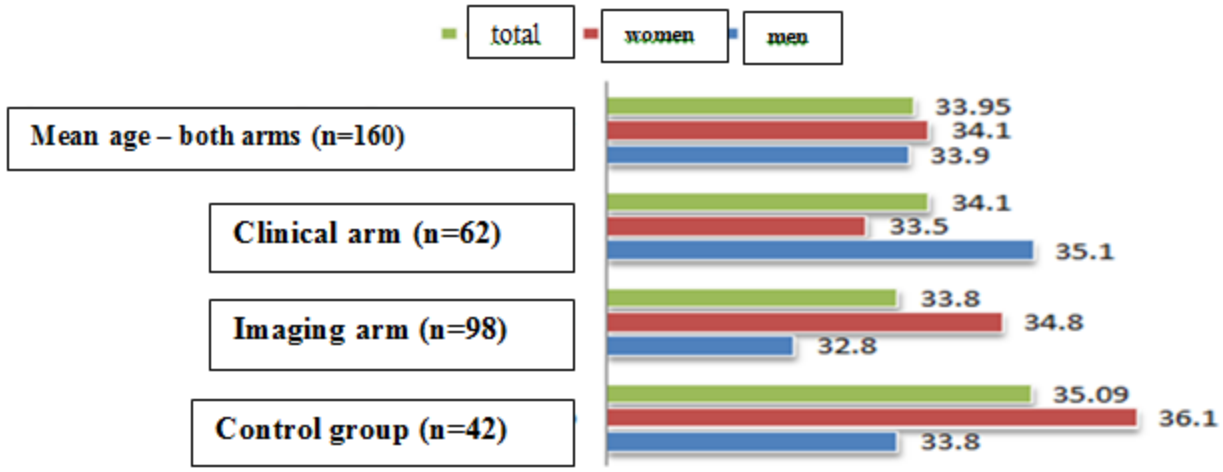


Figure 5: *Presentation by gender total and in the subgroup of nr-ax SpA:*



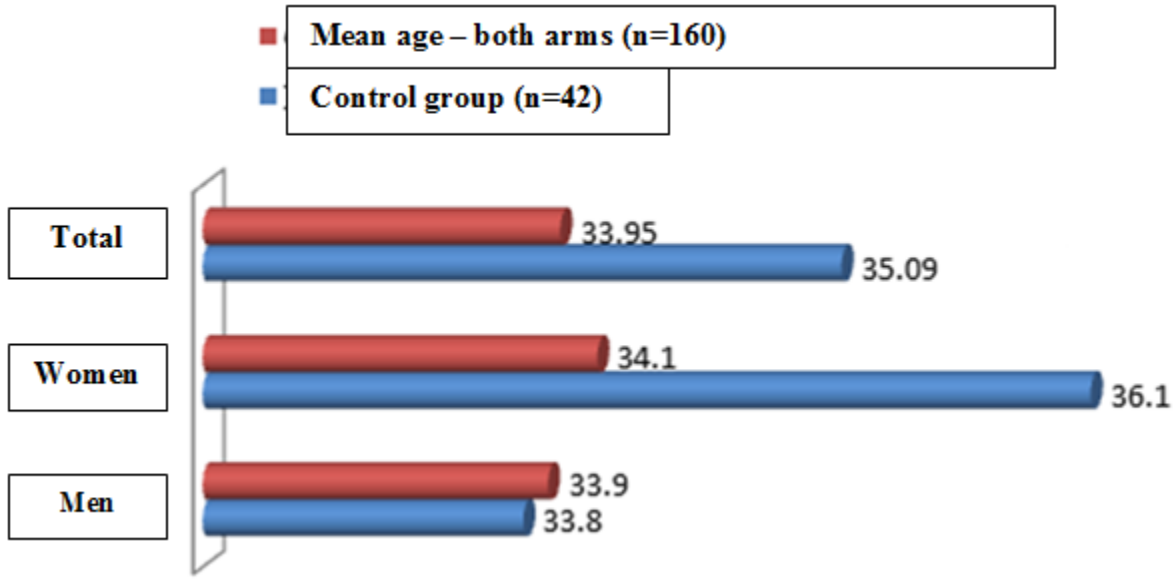
V.1.3 Distribution of patients by age:

Figure 6: *Average* ***age*** *of research participants:*



The mean age of patients in **the imaging arm** was 33.8 ± 7.71, compared to the mean age of patients in **the clinical arm** of 34.12 ± 6.95 and **the control group** of 35.09 ± 7.9 (p> 0.05). Figure 10 presents data on the mean age depending on gender and in the individual groups of patients and the control group.

Figure 7: Mean age *of the group among* ***men and women*** *in the group of patients with nr-ax SpA and the control group:*



We found a mean age of men and women with nr-ax SpA of 33.9 ± 6.5 years and 34.1 ± 7.2 years, respectively (mean for both sexes 33.95 ± 7.4 years). In the control group, the mean age was 33.8 ± 6.8 for men and 36.1 ± 7.35 for women (mean for both sexes in the control group 35.09 ± 7.9 years).

V.1.4 Distribution by duration of symptoms (in years) in the groups of patients in the imaging and clinical arm, as well as in the control group:

The non-radiographic phase of spondylarthritis is characterized by a short duration of symptoms, which usually develop smoothly over time. Usually, the diagnosis of the disease takes place between the third month and the third year from the onset of symptoms. The mean duration of inflammatory low back pain in the nr-ax SpA group was 0.625 g ± 0.23. Statistically significant longer duration of symptoms was observed in the **control group** - 1.179 years ± 0.33, with a median of 1.1 years ($p < 0.05$). The data from the descriptive analysis are presented in Table 2:

Table 2: *The values of the average* ***duration of symptoms (in years)*** *in patients with Nr-ax SpA and the control group are presented:*

Group patients	Mean duration (years)	Median	±SD	Min	Max
Nr-ax SpA(n=160)	**0.625**	0.8	±0.23	0.2	1.6
Control group (n = 42)	**1.179**	1.1	±0.3353	0.5	2.1

The following figure graphically depicts the average duration of symptoms (in years) in the three groups and their median - Figure 8:

Figure 8: *Presentation of the mean duration of symptoms in patients from the* ***two subgroups of Nr-ax SpA*** *and* ***the control group*** *(with specified median)****:***

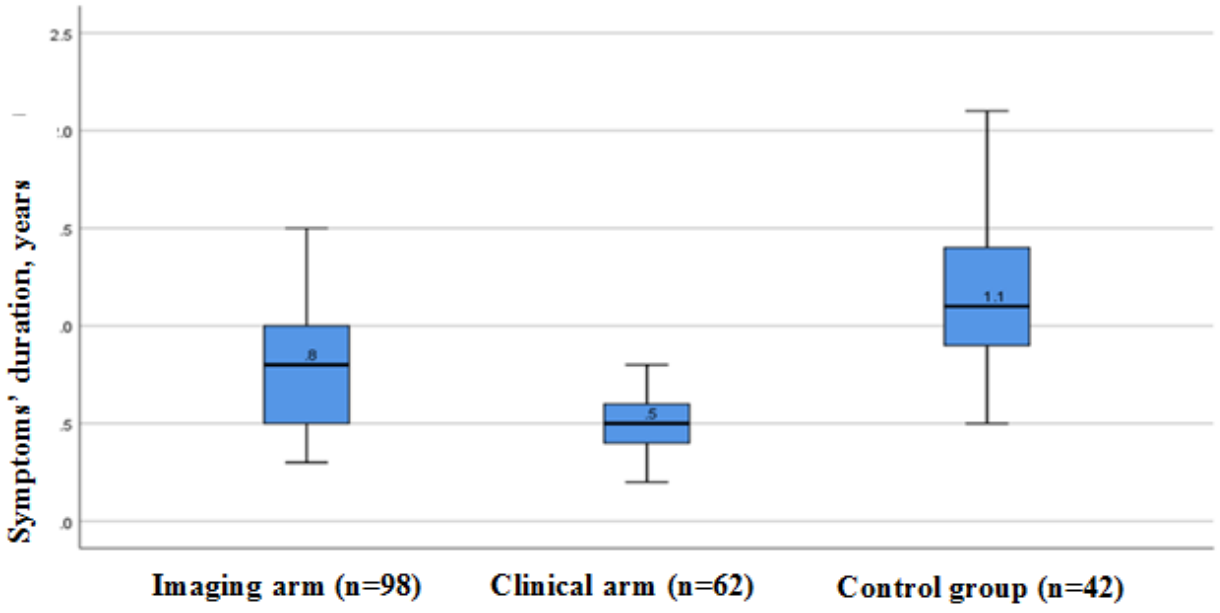


Table 3: *Distribution by* ***duration of symptoms (in years)*** *in the groups of patients in the imaging and clinical arm, as well as in the control group* ***by sex****:*

Group patients		Mean duration (years)	Median (years)	±SD	Min	Max	p
Imaging arm	**men**	0.725	0.7	±0.28	0.3	1.5	**p>0.05**
	women	0.806	0.8	±0.24	0.5	1.5	
Clinical arm	**men**	0.51	0.5	±0.12	0.3	0.8	**p>0.05**
	women	0.47	0.5	±0.13	0.2	0.8	
Control group	**men**	1.24	1.3	±0.32	0.7	2.0	**p>0.05**
	women	1.12	1.0	±0.34	0.5	2.1	

We found similar duration of symptoms before diagnosis in the two subgroups of Nr-ax SpA (imaging and clinical shoulders) and the control group of participants (p> 0.05). Similar results were observed when considering the average duration of inflammatory back pain in both sexes in each subgroup and group of patients. (p> 0.05).

V.2 Evaluation of clinical and laboratory disease activity in patients with nr-ax SpA for both sexes and the control group.

V.2.1 Evaluation of laboratory markers of inflammation involved in the formation of disease activity

Table 4: *The average values of the* ***erythrocyte sedimentation rate (ESR)*** *in mm/h in patients from the imaging and clinical arm of nr-ax SpA and the control group are presented:*

Group patients	Mean ESR mm/h	Median	±SD	Min	Max
Imaging arm (n=98)	42.2	36.5	±20.86	10.0	120.0
Clinical arm (n = 62)	32.51	30.0	±8.79	13.0	70.0
Control group (n = 42)	15.07	15.0	±6.512	5	29

The upper reference value of the ESR standard was 28 mm/h used in other studies in the medical literature, and up to 5 mg/l for the C-reactive protein. In the group of patients with nr-ax SpA, 10.2% had ESR <28 mm/h and 31.63% CRP was below the upper reference value of 5 mg/l. In the clinical arm, normal values were 27.4% for ESR and 45.1% for CRP, respectively. The majority of participants in the control group demonstrated values of acute-phase indicators below the upper reference value - 92.8% for ESR and 85.7% for CRP. Средната стойност на СУЕ в общата група на болните от nr-ax SpA е 37.35мм/ч ± 14.6. При CRP, тази стойност е 10.93мг/л±6.2.

Figure 9: *Mean value of* ***erythrocyte sedimentation rate (ESR)*** *in mm/h in the group of patients with nr-ax SpA and in its two subgroups:*	***Figure 10:*** *Mean value of* ***C-reactive protein (CRP)*** *in mg/l in the group of patients with nr-ax SpA in both subgroups:*

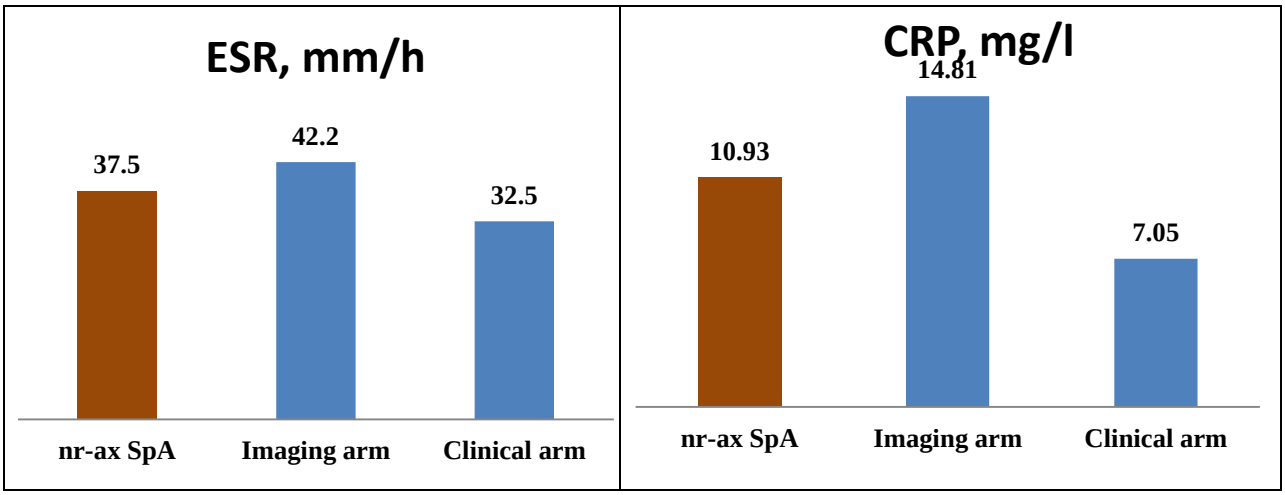


Table 5: *Presented on the average values of C-reactive protein (CRP) (mg/l) in the groups of patients with imaging, clinical arm and control group for both sexes:*

Groups	C-reactive protein (CRP) mg/l	Median	±SD	Min	Max
Imaging arm (n=98)	14.81	7.27	28.59	0.04	193
Clinical arm (n = 62)	7.05	5.65	10.04	0.02	70.7
Control group (n = 42)	2.91	2.14	3.13	0.01	17.2

Several comparative analyzes between the groups of patients with imaging and clinical arms were performed using **the t-test for independent samples with different variances**. The comparison of mean values can be applied after check the hypothesis for equality of variances and the null hypothesis (Ho) is rejected, ie the difference between variances is significant:

Hypothesis:

Ho: $\mu_1 = \mu_2$

H1: $\mu_1 \neq \mu_2$

Subgroup comparison between the mean values of acute phase reactants (CRP in mg/l and ESR in mm) in groups of patients with nr-ax SpA imaging and clinical arm and comparison of the general group of patients and the control group (basic data from the comparisons and details of the statistical model):

Tables 6 and 6a: *Comparative analysis of the mean* ***CRP values (mg/l)*** *in the two subgroups of patients with Nr-ax SpA -* ***imaging and clinical arm:***

Group	N	Mean	Std deviation	Std error
CRP – imaging arm	98	14.8163	28.59193	2.88822
CRP – clinical arm	62	7.0532	10.04277	1.27543

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
CRP	Equal variances assumed	7.011	.009	2.057	158	.041	7.76310	3.77379	.30952	15.21668
	Equal variances not assumed			2.459	130.622	.015	7.76310	3.15730	1.51704	14.00916

Tables 7 and 7a: *Comparative analysis of mean* ***CRP values (mg/l)*** *between the general group of patients with* ***Nr-ax SpA and the control group:***

Group	N	Mean	Std deviation	Std error
CRP – nr-ax SpA	160	11.8081	23.49069	1.85710
CRP – control group	42	2.9238	3.13040	.48303

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
CRP	Equal variances assumed	7.896	.005	2.441	200	.016	8.88432	3.63967	1.70725	16.06138
	Equal variances not assumed			4.630	178.080	.000	8.88432	1.91889	5.09762	12.67101

P-value = 0.015 and is less than α = 0.05, which gives us reason to reject the null hypothesis in favor of H1 and to assume that in the subgroup of patients with the image arm of nr-ax SpA, CRP has a statistically significant -high average. The comparison between the mean CRP values in the general group of patients with nr-ax SpA (both arms) compared to the control group was also statistically significantly higher (p = 0.00).

Tables 8 and 8a: *Comparative analysis of the mean values of* ***ESR (mm/h)*** *in the two subgroups of patients with Nr-ax SpA -* ***imaging and clinical arm:***

Group	N	Mean	Std deviation	Std error
СУЕ – imaging arm	98	42.20	20.864	2.108
СУЕ– clinical arm	62	32.52	8.796	1.117

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ESR	Equal variances assumed	11.422	.001	3.463	158	.001	9.688	2.797	4.163	15.213
	Equal variances not assumed			4.061	141.409	.000	9.688	2.385	4.972	14.404

Tables 9 and 9a: *Comparative analysis of the mean values of* ***ESR (mm/h)*** *between the general group of patients with* ***Nr-ax SpA and the control group:***

Group	N	Mean	Std deviation	Std error

ESR – nr-ax SpA	160	38.5	17.823	1.409
ESR– control group	42	15.07	6.512	1.005

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ESR	Equal variances assumed	7.839	.006	8.343	200	.000	23.379	2.802	17.853	28.904
	Equal variances not assumed			13.508	180.650	.000	23.379	1.731	19.964	26.793

The analysis showed a statistically significantly higher mean ESR in the group of patients with nr-ax SpA (p = 0.00), as well as in the general group of patients compared to the control group (p = 0.00).

As expected, patients with inflammatory joint disease present with higher values of acute phase reactants, compared to healthy individuals or patients with non-inflammatory nature of joint disease. It is important to note that both routinely tested laboratory markers for inflammatory activity are statistically significantly higher in the group of patients in whom bone marrow edema is objectified by SIJs MRI.

V.2.2 Clinical assessment of disease activity in nr-ax SpA and control group: Mean values ± standard deviation (SD) of the indices for assessment of total disease activity, degree of functional impairment, axial structural impairment, quality of life and level BME on MRI of the SIJs are presented with their average values in the studied groups and subgroups of participants in the research in Table 10:

Table 10: *The results of the mean values ± SD of the studied scales for disease activity, functional deficit, quality of life and changes in imaging studies are presented:*

Groups N = 202	**Imaging arm N = 98**	**Clinical arm N = 62**	**Total patients with Nr-ax SpA N = 160**	**Control group N = 42**
BASDAI, Mean±SD	4.1±0.67	4.01±0.78	4.07±0.71	1.76±0.37
BASFI, Mean±SD	5.06±1.28	4.48±1.18	4.84±1.27	2.14±0.5
ASDAS-CRP, Mean±SD	2.31±0.87	2.05±0.52	2.2±0.76	1.16±0.21
ASQoL, Mean±SD	4.79±3.27	5.18±3.03	4.94±3.18	1.38±0.9
BASMI, Mean±SD	0.8±1.1	0.32±0.53	0.61±0.95	0.24±0.43
VAS –patients' report, Mean±SD	55.3±13.4	41.3±12.7	51.9±13.3	19.5±7.19
VAS – phisicians' report, Mean±SD	48.42±12.54	46.71±11.3	45.5±13	22.88±8.4

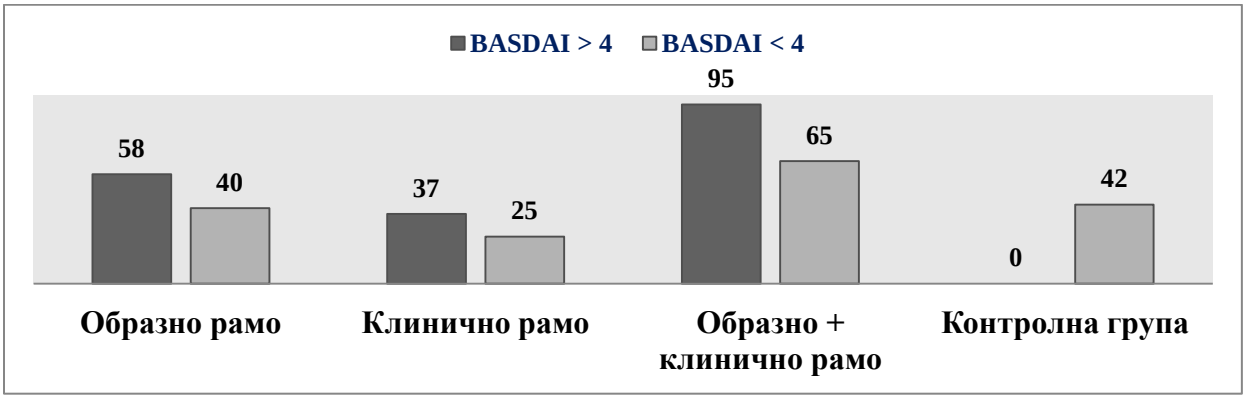
SPARCC, Mean±SD	22.42±15.18	0.15±0.67	13.79±16.1	0
SPARCC minus, Mean±SD	19.38±11.77	0.02±0.1	11.87±13.19	0

Legend: BASDAI - Bath Ankylosing Spondylitis Disease Acivity Index, BASMI – Bath Ankylosing Spondylitis Metrology Index, BASFI – Bath Ankylosing Spondylitis Functional Index, VAS – visual analogue scale, SPARCC - Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system, ASQoL – Ankylosing Spondylitis Quality of Life, ASDAS – CRP – Ankylosing Spondylitis Disease Activity Score (using CRP).

V.2.2.1 Bath Ankylosing Spondylitis Disease Acivity Index – BASDAI

We categorized the patients on the basis of the established values of BASDAI, basically dividing them into two groups - BASDAI> 4 and BASDAI <4. It is generally accepted to classify the disease with high disease activity in BASDAI> 4. 59.2% of patients in the imaging arm and 59.7% of patients in the clinical arm present with nr-ax SpA activity (for the total group nr-ax SpA are 59.3%). In the control group all patients fall into the category BASDAI <4.

Figure 11: *Distribution by number of patients according to BASDAI in the individual groups -* ***imaging, clinical arm, all patients with nr-ax SpA and the control group****:*



Tables 11 and 11a: *Main values of the comparative analysis between the mean values of* ***BASDAI*** *in the two groups of patients and details of the statistical model:*

Group	N	Mean	Std deviation	Std error
BASDAI – imaging arm	98	4.107	.6742	.0681
BASDAI– clinical arm	62	4.015	.7867	.0999

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
BASDAI	Equal variances assumed	1.801	.181	.793	158	.429	.0926	.1168	-.1380	.3233
	Equal variances not assumed			.766	115.203	.445	.0926	.1209	-.1469	.3321

The clinical disease activity calculated by BASDAI was numerically higher in patients with Nr-ax SpA imaging arm, in the absence of a statistically significant difference in the study groups (p = 0.429). In both subgroups of Nr-ax SpA, despite the presence of acute inflammatory changes in MRI of the SIJs, the mean values of this index for assessing disease activity fall into the category of high degree of disease activity (> 4).

V.2.2.2 Bath Ankylosing Spondylitis Functional Index -BASFI

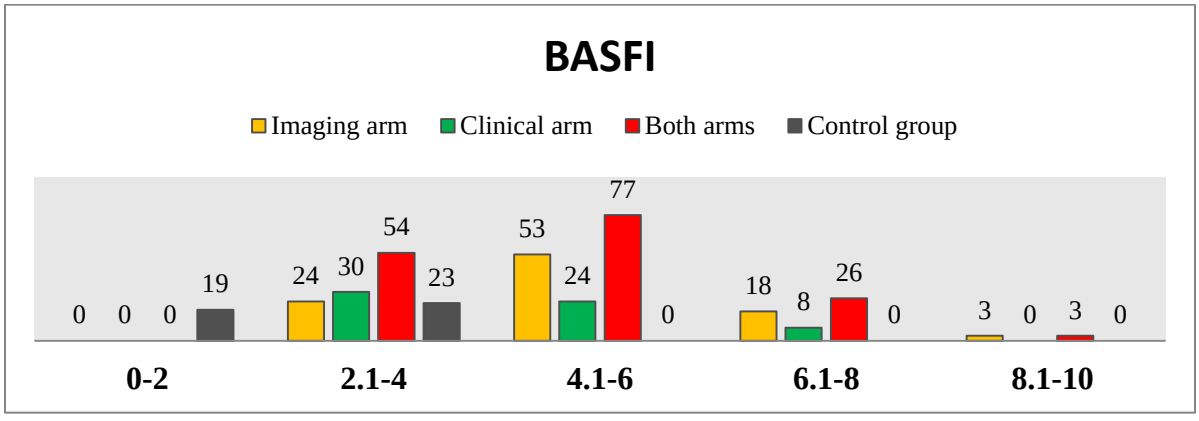
The largest relative share of patients with nr-ax SpA are with BASFI between 4.1 and 6.0 - 48.1%. In the same category of the index the patients from the imaging arm of the disease predominate, compared to those from the clinical arm - 68.8% against 31.2%.

A high value of the clinical assessment of physical function > 6.1 was observed in 29 patients with nr-ax SpA (18.1%). In the BASFI range from 6.1 to 8.0, patients with the imaging arm predominate - 69.2% compared to 30.8% of patients with the nr-ax SpA clinical arm. Our results show a greater degree of functional impairment in those patients who have MRI data for inflammation of the sacroiliac joints.

At the same time, we did not register patients with Nr-ax SpA in both subgroups, with no or low degree of functional impairment, ie. BASFI averages less than 2.1.

In the control group the predominant relative share of patients with clinical assessment of physical function up to 4 - respectively 45.2% in the category BASFI 0-2 and 54.8% in the category BASFI 2.1 - 4.

Figure 12: *Distribution by number of patients (N) according to* ***BASFI*** *in the individual groups* ***- imaging, clinical arm, all patients with nr-ax SpA and the control group:***



Tables 12 and 12a: *Comparative analysis of the mean* ***BASFI*** *values in the two subgroups of patients with Nr-ax SpA and details of the analysis:*

Group	N	Mean	Std deviation	Std error
BASFI – imaging arm	98	5.07	1.283	.130
BASFI – clinical arm	62	4.48	1.190	.151

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
BASFI	Equal variances assumed	.423	.517	2.895	158	.004	.586	.202	.186	.986
	Equal variances not assumed			2.945	137.079	.004	.586	.199	.193	.980

The level of functional impairment calculated by **BASFI** had significantly higher mean values in patients with the nr-ax SpA from the imaging arm compared to patients in the clinical arm ($p = 0.004$).

V.2.2.3 Ankylosing Spondylitis Disease Activity Score - ASDAS-CRP

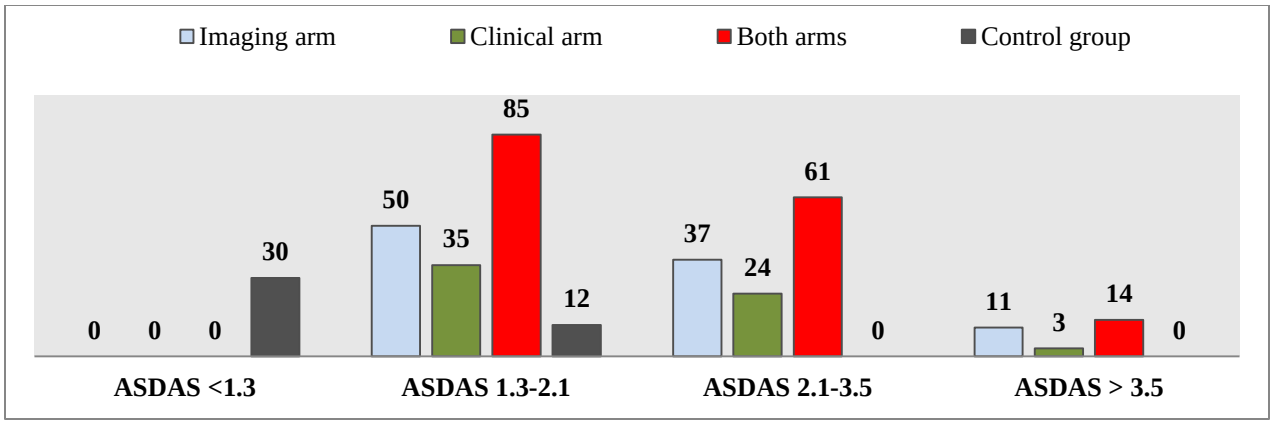
One of the indices for assessing the disease activity in spondyloarthritis is **ASDAS.** We used its variant of calculation, using the CRP values, which is preferred by a number of authors to the variant using the ESR values.

For the purposes of the analysis of the obtained results we used the generally accepted classification of ASDAS by categories of disease activity: **<1.3 - inactive, 1.3-2.1 - with moderate activity, 2.1 - 3.5 - high and over 3.5 with very high disease activity**. There are no patients with nr-ax SpA who fall into the category of inactive disease.

Most of them reveal ASDAS - CRP, which defines them as patients with moderate (53.1%) and high disease activity (38.1%). Only 8.75% of patients with nr-ax SpA have very high activity of the underlying disease.

Impressive is the higher relative share of patients with ASDAS - CRP in the categories of moderate, high and very high activity group in the imaging arm compared to patients with the clinical arm - respectively. 27.5% vs 19.2% (ASDAS-CRP 1.3-2.1), 30.3% vs 19.67% (ASDAS-CRP 2.1-3.5) and 39.28% vs 10.7% (ASDAS-CRP> 3.5) ***(Figure 13):***

Figure 13: *Distribution of patients in the studied groups and subgroups according to the different categories of* ***ASDAS - CRP*** *(number of patients):*



Tables 13 and 13a: *Comparative analysis of the mean values of* ***ASDAS - CRP*** *in both groups of patients and details of the analysis:*

Group	N	Mean	Std deviation	Std error
ASDAS-CRP – imaging arm	98	2.301	.8743	.0883
ASDAS-CRP – clinical arm	62	2.055	.5284	.0671

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ASDAS_CRP	Equal variances assumed	7.126	.008	1.997	158	.048	.2462	.1233	.0027	.4897
	Equal variances not assumed			2.219	157.733	.028	.2462	.1109	.0271	.4653

Patients with nr-ax SpA with MRI changes of the SIS have higher mean values of the clinical index of disease activity - ASDAS - CRP. ASDAS-CRP was statistically significantly higher in the subgroup of patients from the imaging arm compared to patients without MRI data for BME (p = 0.028).

Degrees of correlation between laboratory indicators of inflammation and clinical rates of disease activity:

For the group of patients from the imaging arm, we used the Scatter plots methodology and found that there was no linear dependence between the set variables (BASDAI, BASFI and ASDAS-CRP) on the acute phase marker CRP. Therefore, we used nonparametric correlation tests.

Table 14: *Correlation between CRP, BASDAI, BASFI and ASDAS-CRP in the group of patients from the imaging arm (N = 98):*

			BASDAI	CRP	BASFI	ASDAS_CRP
Kendall's tau_b	**BASDAI**	Correletion coefficient		.249**	.246**	.265**

	CRP	Correletion coefficient	.249**		.225**	.477**
	BASFI	Correletion coefficient	.246**	.225**		.239**
	ASDAS_CRP	Correletion coefficient	.265**	.477**	.239**	
Spearman's rho	**BASDAI**	Correletion coefficient		.350**	.350**	.360**
	CRP	Correletion coefficient	.350**		.315**	.651**
	BASFI	Correletion coefficient	.350**	.315**		.325**
	ASDAS_CRP	Correletion coefficient	.360**	.651**	.325**	

***Statistically significant correlation at level of 0.01 (2-tailed).*

There is a statistically significant positive relationship between every two pairs of variables. The correlation between CRP and BASDAI is moderate (correlation coefficient **0.24,** p <0.05).

Between CRP and BASFI with a correlation coefficient of **0.22** it is also moderate with a degree of significance p <0.05, and between the variables CRP and ASDAS-CRP it is moderate to strong (correlation coefficient **0.65**, p <0.01).

Correlation dependences between acute phase reactants and clinical indices of disease activity in the overall group of patients with nr-ax SpA:

We investigated the correlation between laboratory indicators of inflammation (ESR and CRP) and the scores for determining disease activity in nr-ax SpA. **There is a statistically significant positive relationship between each of the two variables.**

The strongest relationship is between **CRP and ASDAS - CRP** with a correlation coefficient of 0.39, p = 0.00 and **CRP with BASDAI** - 0.24, p = 0.00. The correlation coefficients between **ESR - BASDAI** and **ESR - ASDAS - CRP** are 0.25, p = 0.00 and 0.15, p = 0.007, respectively. Details of the analysis and other correlation coefficients of the studied clinical and laboratory markers can be seen in ***Table 15.***

Table 15: *Correlation matrix of dependence between the considered* ***laboratory markers of inflammation*** *and* ***the clinical indices for assessment of disease activity*** *in nr-ax SpA, n = 160:*

		ESR	**CRP**
BASDAI	Correletion coefficient	.253**	.242**
	Sig.(2-tailed)	.000	.000
	N	160	160
ASDAS_ CRP	Correletion coefficient	.151**	.393**
	Sig.(2-tailed)	.007	.000
	N	160	160
VAS patient	Correletion coefficient	.167**	.166**
	Sig.(2-tailed)	.003	.002
	N	160	160
VAS phisician	Correletion coefficient	.156**	.139*
	Sig.(2-tailed)	.005	.011
	N	160	160

***. Statistically significant correlation at level of 0.01 (2-tailed).*

**. Statistically significant correlation at level of 0.05 (2-tailed).*

V.2.2.4 Assessment of the total level of disease activity according to the visual analogue scale (VAS) according to the patient/doctor (mm):

The mean level of assessment of the total level of disease activity **according to the patient** for the whole group of patients with nr-ax SpA is 51.99 ± 13.3 with a calculated median of 50. The minimum VAS score reported by the patient is 15 mm and the maximum - 90 mm.

Patients in the nr-ax SpA imaging arm had higher mean VAS scores than patients in the clinical arm (55.34 ± 13.42 vs. 46.71 ± 11.32), although there was no statistically significant difference (p> 0.05).

Table 16: Mean VAS scores - Patient assessment of overall disease activity level:

Group	VAS – patient assessment (mm)	Median	±SD	Min	Max
Imaging arm (n=98)	55.34	54.0	±13.42	15	90
Clinical arm (n = 62)	46.71	45.0	±11.32	22	80
Nr-ax SpA (n = 160)	51.99	50.0	±13.3	15	90
Control group (n = 42)	22.88	20.5	±8.42	10	42

The results of the **doctor's assessment** of the total level of disease activity in the group of patients with nr-ax SpA show average values of 45.5 ± 13.07. The average levels of VAS according to the doctor are analogous to the previous data higher in patients with imaging arm compared to clinical (48.48 ± 12.54 vs. 41.13 ± 12.72) in the absence of statistical significance between subgroups (p> 0.05). In the control group of patients the mean values of VAS were 19.55 ± 7.19, in the median 19.5 and with a level of significance compared to patients with nr-ax SpA (including subgroups) p <0.05.

***Table 17:** Mean values of **VAS results - Physician's assessment** of the overall level of disease activity:*

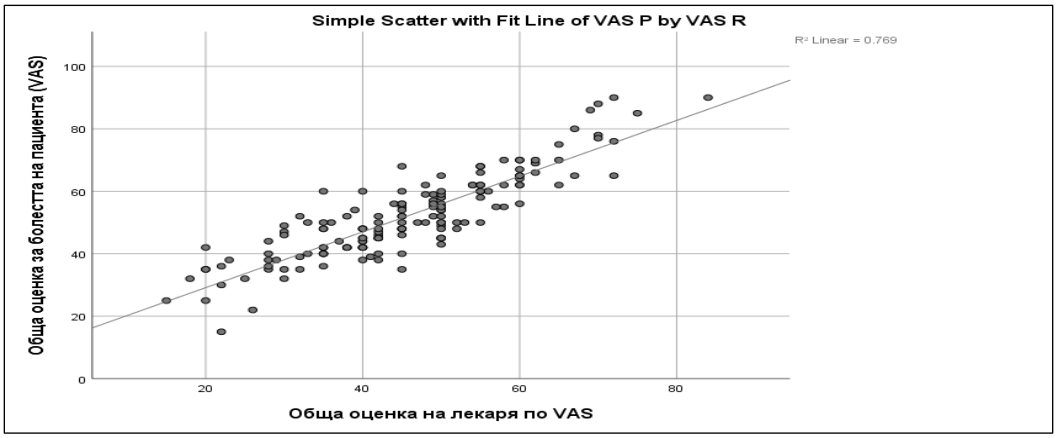
Group	VAS – Physician's assessment (mm)	Median	±SD	Min	Max
Imaging arm (n=98)	48.42	48.4	±12.54	15	84
Clinical arm (n = 62)	41.13	42	±12.72	20	72
Nr-ax SpA (n = 160)	45.59	45	±13.07	15	84

Control group (n = 42)	19.55	19.5	±7.19	8	42

The overall assessment of patient VAS disease activity according to the patient and the physician is usually related, although in most cases the mean values according to the patient are higher than those reported in the physician evaluation.

We found **a strong correlation** between the mean values of the overall assessment of disease activity according to the patient and the doctor in the group of patients with nr-ax SpA, **R = 0.769**, p <0.01, *(Figure 14):*

Figure 14: *Graphical representation of the positive correlation between the values of total disease activity (VAS) according to the patient and the doctor**:***



We used **the t-test for independent samples with different variances** and compared the mean values of the clinical indices for disease activity (via BASDAI and ASDAS-CRP) and the score for the assessment of functional impairment (using BASFI). in the groups of patients with **nr-ax SpA (total for imaging and clinical arm)** and **the control group**.

We found statistically significantly higher average values for each of the studied parameters.

The mean values of BASDAI in patients with nr-ax SpA were 4.071 ± 0.71 compared to 1.762 ± 0.37 in the control group of patients (p <0.05).

The mean values of the clinical assessment of the functional status of BASFI in patients with nr-ax SpA is 4.84 ± 1.27 with a level of statistical significance p <0.05 compared to the control group of patients with BASFI 2.14 ± 0.5.

The results are similar for the second index for assessment of disease activity - ASDAS, calculated with CRP, as the data from the descriptive statistics are presented in *Table 18.*

Table 18: *Data from the comparative analyzes between patients with nr-ax SpA and the control group regarding the indices for assessment of disease activity* ***(BASDAI and ASDAS-CRP)*** *and functional impairment* ***(BASFI):***

Group	N	Mean	Std deviation	Std error	p
BASDAI – nr-ax SpA	160	4.071	.7189	.0568	**p<0.05**
BASDAI – control group	42	1.762	.3780	.0583	

BASFI – nr-ax SpA	160	4.84	1.276	.101	**p<0.05**
BASFI – control group	42	2.14	.503	.708	
ASDAS-CRP – nr-ax SpA	160	2.206	.7668	.0606	**p<0.05**
ASDAS- CRP – control group	42	1.160	.2119	.0327	

Patients with Nr-ax SpA, regardless of the presence/absence of BME from MRI of SIJs, have statistically significantly higher disease activity (via BASDAI and ASDAS-CRP) and a greater degree of functional impairment (via BASFI) compared to control group.

V.2.3 Clinical assessment of the level of spinal cord injury in nr-ax SpA (including intragroup in imaging and clinical arm) and control group:

V.2.3.1 Bath Ankylosing Spondylitis Metrology Index –BASMI

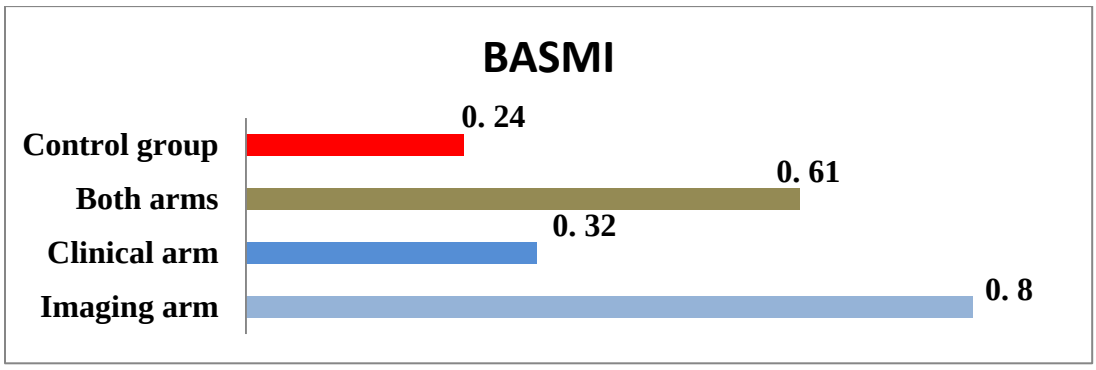
Nr-ax SpA is characterized by a short duration of symptoms, resp. with predominantly inflammatory changes in the affected joint structures. The degree of spinal cord injury is a function of the level of inflammatory activity and the duration of symptoms. This suggests a relatively lower degree of permanent structural changes in patients with Nr-ax SpA.

To determine the degree of spinal cord injury in nr-ax SpA, we used the recommended ASAS composite index BASMI. BASMI = 0 indicates no restrictions on the volume of movement in the axial skeleton, while BASMI = 10 means very limited volumes of movement in the spine.

The mean values of BASMI in the two subgroups of patients with nr-ax SpA were 0.8 ± 1.1 for the imaging arm and 0.32 ± 0.53 for the clinical arm ($p < 0.05$) and 0.61 ± 0.95 for the whole group of patients with nr-ax SpA.

We found a statistically significant difference with the mean values of BASMI in the control group, where its values were 0.24 ± 0.43 ($p < 0.05$).

Figure 15: Mean BASMI values in subgroups and groups:



V.2.4 Assessment of changes in the sacroiliac joints (SIJ) by magnetic resonance imaging (MRI):

V.2.4.1 By assessing the extent of bone marrow edema according to the requirements of a positive MRI protocol in sacroiliitis (acute sacroiliitis):

The changes to the SIJ by SPARCC and SPARCC minus used in the evaluation analysis are one of the ways to early detect nr-ax SpA and differentiate the group of patients from the imaging arm. The two scores differ in the lack of assessment of the "intensity" and "depth" of the registered areas of bone marrow edema (BME) in the presence of sacroiliitis.

Despite the differences, SPARCC and SPARCC minus showed a **strong correlation with a coefficient = 0.97**, p <0.05 ***(Figure 16).***

Figure 16: *Graphical representation of the correlation relationship between SPARCC and SPARCC - minus:*

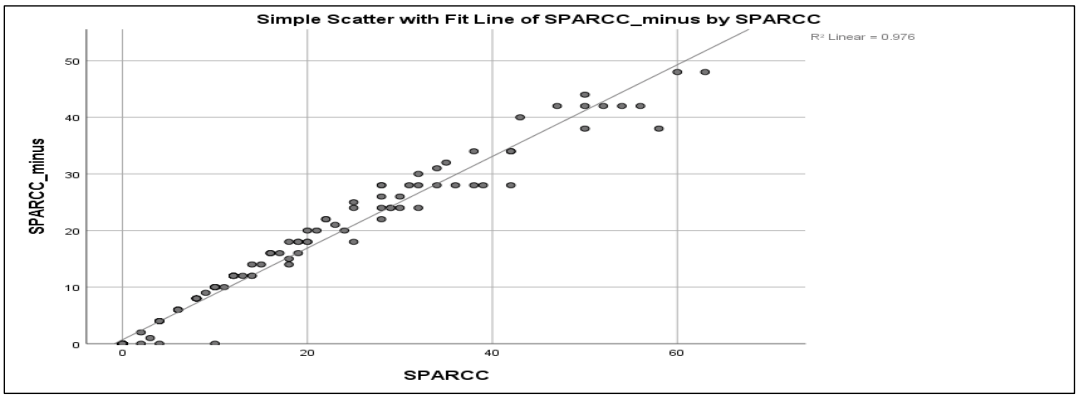


Table 19 *Descriptive analysis of SPARCC in the individual subgroups of nr-ax SpA and the control group:*

Patient group	SPARCC	Median	±SD	Min	Max
Imaging arm (n=98)	22.42	18.5	±15.18	2	63
Clinical arm (n = 62)	0.15	0	±0.674	0	4
Total group with nr-ax SpA (n = 160)	13.79	8.5	±16.1	0	63
Control group (n = 42)	NA	NA	NA	NA	NA

The mean SPARCC score in patients with Nr-ax SpA imaging arm was 22.42 ± 15.18 (minimum score 2 and maximum 63). Clinical arm patients presented with discrete minor changes in SIJ on MRI - mean SPARCC values in the Nr-Ax SpA clinical arm subgroup 0.15 ± 0.674. ***(Table 19)***

Table 20**:** *Descriptive analysis of SPARCCminus in the individual subgroups of nr-ax SpA and the control group:*

Patient group	SPARCC minus	Median	±SD	Min	Max
Imaging arm (n=98)	19.38	17	±11.77	0	48
Clinical arm (n = 62)	0.02	0	±0.127	0	1
Total group with nr-ax SpA (n = 160)	11.88	8.0	±13.19	0	48
Control group (n = 42)	NA	NA	NA	NA	NA

Similar to the previous data from the SPARCC calculations in the individual groups, are the results of the SPARCC minus score (this does not include the "depth" and "intensity" components of the signal). The mean SPARCC minus score from the imaging arm of Nr-ax SpA patients was 19.38 ± 11.77 (minimum score 0 and maximum 48).

Tables 21 and 21a: *Comparative analysis of the incidence of SIJ BME by SPARCC in the two subgroups of patients with Nr-ax SpA:*

Group	N	Mean value	Standard deviation	Standard error
SPARCC imaging arm	98	22.42	15.183	1.534
SPARCC clinical arm	62	.15	.674	.086

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
SPARCC	Equal variances assumed	130.533	.000	11.531	158	.000	22.273	1.932	18.458	26.088
	Equal variances not assumed			14.500	97.603	.000	22.273	1.536	19.225	25.322

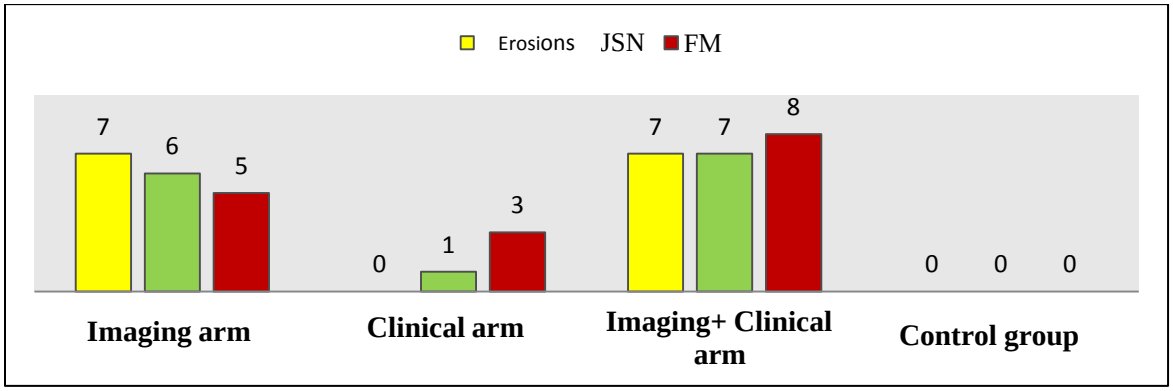
When comparing the mean changes in the sacroiliac joints (SIJ) using the SPARCC scoring system, we found statistically significant changes in patients with the nr-ax SpA imaging arm compared to the clinical arm ***(p = 0.00).***

V.2.4.2 Due to the presence of erosions, narrowing of the joint space and areas of bone marrow metaplasia in nr-ax SpA (including intragroup in the imaging and clinical arm) and the control group:

In addition to the presence of bone marrow edema (BME), when analyzing the results of magnetic resonance imaging of the SIJ, the presence of chronic structural changes - erosive changes, narrowing of the joint space (JSN) and bone marrow metaplasia - FM). The presence

of these changes in the context of SpA means previous episodes of acute sacroiliitis. All erosions, JSN and FM are combined with BME. Both bone marrow edema and chronic changes were found in patients within the imaging arm, with few exceptions of discrete changes in four patients within the clinical arm. Precisely due to the poor performance of BME, these patients were distributed in the group of clinical and not the imaging arm of nr-ax SpA. The relative share of patients with erosive changes in the imaging arm is 7.14% (n = 7), with narrowing of the joint space 7.14% (n = 7), and with FM - 5.10% (n = 5) ***(Figure 17).*** In one patient with Nr-ax SpA - clinical arm, a narrowing of SIJ space was registered (1.61%), and in three - bone marrow metaplasia (4.83%).

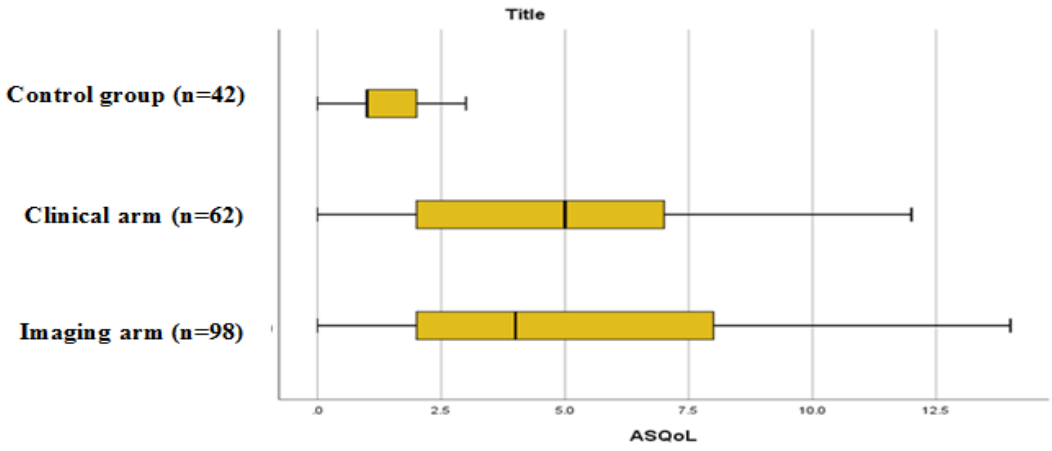
Figure 17: Frequency of the established structural changes of MRI of SIJ- ***erosions, narrowed joint spaces and bone marrow metaplasia*** in the separate groups / subgroups of patients and the control group (number of patients, n):



V.2.5 Assessment of quality of life using the ASQoL disease-specific questionnaire for nr-ax SpA (including subgroup in imaging and clinical arm) and control group:

The mean value of ASQoL in patients in the imaging arm nr-ax SpA 4.79 ± 3.27 with a median of 4.0, while in the group of patients in the clinical arm - 5.18 ± 3.03 and a median of 5.0. These values together with the results of the control group are shown in **Figure 18.**

Figure 18: *Presentation of the mean levels of ASQoL (with median) in patients with Nr-ax SpA - clinical and imaging arms and participants in the control group:*



- We performed a correlation analysis to verify the statistical relationship between quality of life (measured by the ASQoL questionnaire) and the main parameters for laboratory and clinical disease activity. All correlation dependences show statistical significance at a confidence level of $p < 0.05$. We found a moderate correlation between ASQoL and BASDAI (0.35, $p = 0.001$) and ASQoL and ASDAS - CRP (0.44, $p = 0.036$). Similar positive dependencies are demonstrated by the other variables included in the analysis **(Table 22):**

***Table 22**: Correlation relationships between quality of life indicator (ASQoL) and clinical and laboratory markers of disease activity in nr-ax SpA (n = 160):*

Kendall's tau_b		ESR	CRP	BASDAI	ASDAS_CRP	VAS P	VAS R
ASQoL	Correlation coefficient	.269*	.352**	.365**	.441*	.328**	.290**
	Sig.(2-tailed)	**.03**	**.001**	**.000**	**.036**	**.000**	**.000**
	N	160	160	160	160	160	160

** .Statistically significant correlation at 0.01 (2-tailed) level.*
** .Statistically significant correlation at the level of 0.05 (2-tailed).*

- The same correlation analysis was applied to the patients in the control group (N = 42), where no positive correlation was found for any pair of variables according to the analysis of Kendall's tau_b ($p > 0.05$).

We performed a correlation analysis to assess the dependencies of the changes in the sacroiliac joints, assessed by SPARCC and the main parameters for the assessment of the disease, incl. quality of life. This analysis includes only patients from the imaging arm presenting with acute lesions in the sacroiliac joints (SIJ).

***Table 23:** Correlation relationships between SPARCC and quality of life (ASQoL), clinical indices for disease assessment, acute inflammatory markers and functional status in patients with nr-ax SpA imaging arm (n = 98):*

Kendall's tau_b		ESR	CRP	BASDAI	ASDAS_CRP	BASFI	ASQoL
SPARCC	Correlation coefficient	.405*	.490**	.560**	.605**	.442*	.595**
	Sig.(2-tailed)	**.04**	**.000**	**.001**	**.000**	**.004**	**.000**
	N	98	98	98	98	98	98

*** .Statistically significant correlation at 0.01 (2-tailed) level.*
** .Statistically significant correlation at the level of 0.05 (2-tailed).*

We found a statistically significant positive correlation between SPARCC and all indicators included in the analysis in patients from the imaging arm with Nr-ax SpA. The correlation coefficient between **SPARCC and acute phase parameters (ESR and CRP)** shows

a moderate degree of correlation, more pronounced in CRP (r = 0.405, p = 0.04 and respectively r = 0.49, p = 0.00). The results of the analysis show the strongest positive correlation between **SPARCC and ASDAS-CRP** (r = 0.605, p = 0.00) and similar values in **SPARCC and BASDAI** (r = 0.56, p = 0.001). They confirm the link between acute inflammatory changes in the affected joints (SIJ) and the levels of assessment of overall disease activity. The correlation between the degree of manifestation of bone marrow edema by MRI of the SIJ and the level of quality of life of patients (**ASQoL**) (r = 0.595, p = 0.00) is also proved.

- In a ***regression analysis*** we aimed to determine the dependence of quality of life in patients with nr-ax SpA and smoking as a risk factor. We found R2 = 4.2%, ie 4.2% of the total variation of the model depends on the smoking factor, and the remaining 95.8% depends on other factors that are not included in the model. The selected factor is statistically significant with ***p-value = 0.003*** according to the model ASQoL = 3.347 + 1.354 smoking. In smokers ASQoL is 1,354 higher than in non-smokers. If the patient is a smoker with 95% certainty it can be argued that in the general population ASQoL increases in the range of 0.451 and 2.257. Details of the analysis are presented in ***Table 24***:

Table 24*: Regression analysis to verify the relationship between smoking and quality of life in nr-ax SpA (ASQoL):*

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	3.347	.363		9.217	.000	2.631	4.063
	Smoking_status	1.354	.458	.205	2.957	.003	.451	2.257

a. Dependent Variable: ASQoL

V.3 Evaluation of clinical and laboratory disease activity in patients with nr-ax SpA and control group by sex:

V.3.1 Evaluation of laboratory markers of inflammation involved in the formation of disease activity by sex.

Acute-phase indicators show some differences in their values in both sexes, both in patients from the imaging arm and in the group of patients from the clinical arm. The mean values of ESR in men from the imaging arm are higher than those in wo+men, respectively 47.41 ± 25.92 and 36.55 ± 11.16. The data in the group of patients from the clinical arm are reciprocal - here the values of ESR in women are slightly higher - 34.05 ± 9.3 versus 29.91 ± 7.32. CRP values range from 0.08 to 193 in the whole group of patients with nr-ax SpA, and here the trend for higher mean values in men in the imaging and higher values in women in the clinical arm ***(Table 25):***

Table 25: *The mean values of* ***ESR (mm / h)*** *and* ***C-reactive protein (CRP) (mg / l)*** *in the groups of patients with imaging, clinical arm and the control group* ***in men and women*** *are presented****:***

Group	ESR –mean value mm/h	Median (years)	±SD	Min	Max
Imaging arm men	47.41	40	±25.92	10	120

	women	36.55	32	±11.16	25	74
Clinical arm	**men**	29.91	28	±7.32	13	48
	women	34.05	32	±9.3	20	70
Control group	**men**	15.32	16	±6.1	5	28
	women	14.87	14.0	±6.96	5	29
Groups		**C-reactive protein (CRP) mg/l**	**Median (years)**	**±SD**	**Min**	**Max**
Imaging arm	**men**	22.58	9.8	±37.65	0.08	193
	women	6.37	6.2	±6.56	0.04	26.5
Clinical arm	**men**	5.55	5.9	±5.22	0.05	16.6
	women	7.94	5.5	±11.99	0.02	70.7
Control group	**men**	3.15	2.54	±2.64	0.02	11.2
	women	2.71	3.53	±3.53	0.01	17.2

The statistical analyzes performed in the group of patients with nr-ax SpA from the imaging arm found that the male sex has higher mean values of ESR and CRP were statistically significantly higher (p = 0.008 and p = 0.004) ***(Table 26).***

Table 26: *Mean values of acute-phase reactants by sex in the group of patients with nr-ax SpA from the imaging arm*

Group		**N=98**	**Mean value**	**Standard deviation**	**Standard error**	**p**
ESR	men	50	47.41	25.926	3.630	**p= 0.008**
ESR	women	48	36.55	11.164	1.628	
CRP	men	50	22.58	37.654	5.27267	**p = 0.004**
CRP	women	48	6.38	6.562	.95731	

When examining the influence of gender (Independent Samples T-Test) on ESR and CRP, we found a statistically significant difference in the mean values of the two acute phase indicators (p-0.028 and p = 0.01) ***(Table 27):***

Table 27: *Mean values of acute-phase reactants by sex in the general group of patients with nr-ax SpA: imaging and clinical arms:*

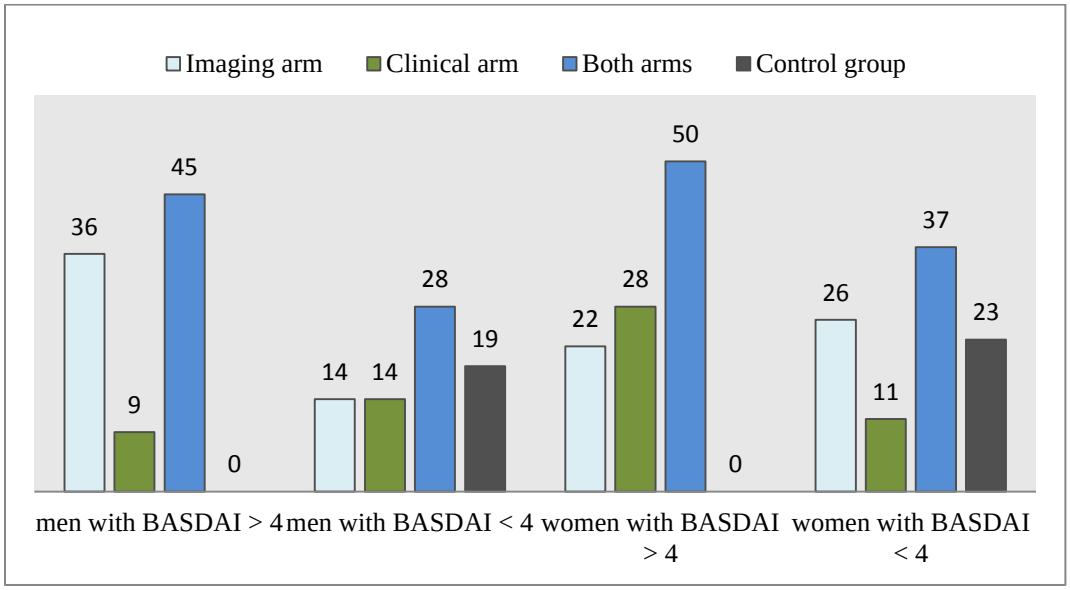
Group		**N=160**	**Mean value**	**Standard deviation**	**Standard error**	**p**
ESR	men	74	41.97	23.304	2.709	**p= 0.028**
ESR	women	86	35.42	10.379	1.119	
CRP	men	74	17.2932	32.28570	3.75314	**p = 0.01**
CRP	women	86	7.0884	9.39546	1.01314	

V.3.2 Clinical evaluation of disease activity in nr-ax SpA and control group by sex:

V.3.2.1 Assessment of disease activity in men and women according to the Bath Ankylosing Spondylitis Disease Activity Index – BASDAI

The predominance of men with nr-ax SpA-imaging arm has a high degree of disease activity, defined as BASDAI over 4, is 72%. The relative share of women with nr-ax SpA-imaging arm with BASDAI> 4 is 45.8%. A total of 61.6% of men with nr-ax SpA have marked signs of the disease according to BASDAI, and in women the relative share is 57.8%. All patients in the control group in both sexes had BASDAI below 4.

Figure 19: *Distribution by* ***number of men and women*** *according to* ***BASDAI*** *in the individual groups nr-ax SpA- imaging arm, clinical arm, total patients and control group (N):*

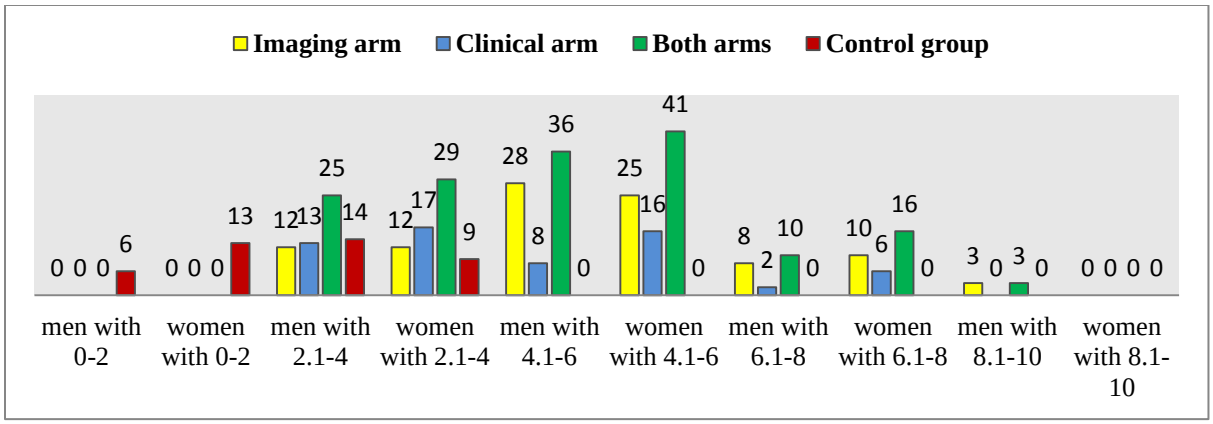


Patients with Nr-ax SpA of both sexes were characterized by a high degree of disease activity detected by BASDAI (> 4) compared to participants in the control group, in which no patient reported BASDAI> 4.

V.3.2.2 Distribution of patients of both sexes according to the Bath Ankylosing Spondylits Functional Index – BASFI

We examined the clinical index of functional impairment in both sexes in all groups with the already used subdivision of BASFI. The sex distribution coincides with that of the previous Figure 16, with Figure 24 showing that men and women with BASFI between 4.1 and 6.0 predominate, ie a high degree of functional impairment during the course of the disease. Patients with nr-ax SpA of both sexes do not fall into the BASFI category from 0.0 to 2.1, and there are no women with BASFI above 8.1. All patients from the control group are presented with values of the functional index up to 4.

Figure 20: *Number of* ***men and*** *women from the different groups and subgroups distributed according to the result of the assessment of functional impairment -* ***BASFI (N):***

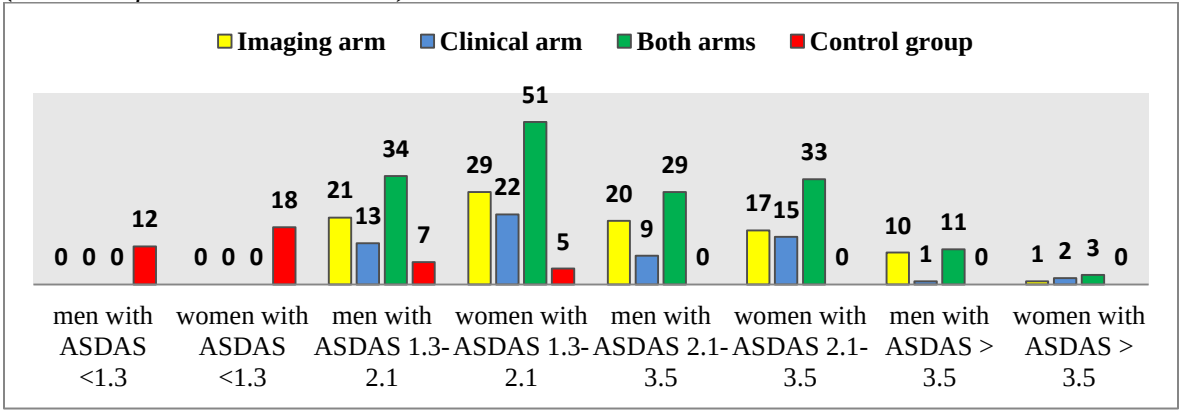


The presented data show that the relative share of patients of both sexes with Nr-ax SpA - imaging arm with BASFI more than 4.1 is higher than men and women than the clinical arm of the disease. BASFI greater than 8.1 has only been reported in men with Nr-ax SpA-imaging arm who have been diagnosed with bone marrow edema from MRI images of the SIJ.

V.3.2.3 Distribution by number of affected men and women of nr-ax SpA in the different categories of the Ankylosing Spondylitis Disease Activity Score - ASDAS-CRP

Of interest are the results of ASDAS values calculated by CRP in patients of both sexes with Nr-ax SpA and the control group. This is due to the incorporation of the values of the laboratory marker for inflammation assessment in this index. The distribution by number of men and women from the different groups and subgroups according to the 4 categories of disease activity according to ASDAS-CRP is presented in the following figure 21. In both categories of ASDAS-CRP ***moderate activity (1.3-2.1) and high disease activity (2.1-3.5), men predominate over women.*** At the same time, a larger number of patients with Nr-ax SpA of both sexes fall into these two stages of assessment of disease activity. In the individual levels of disease activity defined by ASDAS-CRP, a higher number of patients of both sexes was observed in the imaging arm than in the clinical arm of Nr-ax SpA.

Figure 21: *Distribution by* ***sex*** *and index of disease activity assessment -* ***ASDAS-CRP*** *(number of men and women, N):*



The mean values of the indices for the assessment of disease activity BASDAI and ASDAS-CRP are higher in men from the subgroup of the imaging arm of Nr-ax SpA, as well as

in the whole group of patients with Nr-ax SpA (imaging + clinical arm). The same trend is observed in the assessment of the functional status of patients of both sexes in these groups.

Comparative analyses of gender differences in ***BASDAI*** and ***ASDAS-CRP*** were of significant statistical significance (***p = 0.007 and p = 0.004, respectively***) in the ***imaging arm group***. Despite the numerical difference of **BASFI** in favor of male patients, in the same group of patients, there was no statistically significantly higher index of assessment of functional status - ***p = 0.307.***

Table 28: *Comparative analyses **by sex** of the indices for assessment of disease activity (**BASDAI and ASDAS-CRP**) and for functional impairment (**BASFI**) in patients with Nr-ax SpA-imaging arm (N = 98):*

Group	N=98	Mean value	Standard deviation	Standard error	p
BASDAI men	50	**4.282**	.6973	.0976	***p= 0.007***
BASDAI women	48	**3.917**	.5990	.0874	
BASFI men	50	**5.20**	1.435	.201	p = 0.307
BASFI women	48	**4.93**	1.092	.159	
ASDAS – CRP men	50	**2.537**	1.0155	.1422	***p = 0.004***
ASDAS – CRP women	48	**2.045**	.6017	.0878	

The analyses for both sexes, but in **the whole group of patients with Nr-ax SpA**, keep the trend of those in patients with MRI changes of the SIJ (imaging arm), and here the only statistical reliability is the difference in the assessment of the level of disease activity by ASDAS -CRP ***(p = 0.05).***

Table 29*: Gender comparative analyzes of disease activity assessment indices (**BASDAI and ASDAS-CRP**) and functional impairment (**BASFI**) in all patients with Nr-ax SpA (N = 160)*

Group	N=160	Mean value	Standard deviation	Standard error	p
BASDAI men	74	**4.128**	.7665	.0891	p= 0.353
BASDAI women	86	**4.022**	.6759	.0729	
BASFI men	74	**4.94**	1.396	.162	p = 0.376
BASFI women	86	**4.76**	1.166	.126	
ASDAS – CRP men	74	**2.395**	.9245	.1075	***p = 0.05***
ASDAS – CRP women	86	**2.043**	.5549	.0598	

V.3.2.4 Visual Analogue Scale (VAS) - assessment of patient and physician disease activity - intragroup sex distribution in nr-ax SpA and between groups.

The assessment of the level of total disease activity by VAS (**reported by the patient**) by sex in the individual subgroups and groups maintains the tendency for higher absolute mean values in men, as in the already considered indices of disease activity (BASDAI and ASDAS-CRP). ***VAS - according to the patient*** has the highest average values, respectively highest disease activity in patients of both sexes in the imaging arm.

Comparative analyses of ***VAS - reported by the patient*** do not show differences with a significant degree of significance in both sexes, both in the imaging arm (***p = 0.78***) and in the clinical arm (***p = 0.65***).

Each subgroup of patients with Nr-ax SpA, as well as the general group of patients have a higher level of disease activity according to ***VAS - reported by the patient*** compared to the control group of patients in both sexes (***p = 0.03***). Details of the descriptive statistics for VAS - according to the patient are presented in the following table 30:

Table 30*: Descriptive analysis of* ***VAS - Patient assessment*** *of the overall level of disease activity by* ***sex*** *in the individual groups:*

Patient Group		VAS – overall assessment of the patient (mm)	Median (mm)	±SD	Min	Max
Imaging arm	**men**	57.24	55	±15.71	15	90
	women	53.28	52	±10.17	25	77
Clinical arm	**men**	48.61	48	±9.57	35	65
	women	45.59	42	±12.2	22	80
nr-ax SpA total	**men**	54.55	52	±14.59	15	90
	women	49.79	49.5	±11.72	22	80
Control group	**men**	23.47	25	±6.79	10	37
	women	22.39	20	±9.7	10	42

The average values of ***VAS - Physician's assessment*** are numerically lower than those reported by the patient (***p> 0.05***). A similar trend for higher ***VAS - Physician's assessment*** among the male sex, we find when comparing the generalized results in both sexes in the different subgroups of Nr-ax SpA, as well as for the general group of patients with Nr-ax SpA.

There is no statistically significant difference in the overall level of disease activity according to ***VAS - Physician's assessment*** between men and women in the groups (***p> 0.05***).

Statistically significant difference is present when comparing ***VAS - Physician's assessment*** and the control group, both in men (***p = 0.02***) and in women (***p = 0.03***). Detailed data from the descriptive statistics of the analysed indicator for assessment of disease activity by sex in the individual groups are presented in Table 31:

Table 31: Descriptive analysis of ***VAS - Physician's assessment*** of the overall level of disease activity by ***sex*** in the individual groups:

Patient group		VAS – overall Physician's assesment (mm)	Median (mm)	±SD	Min	Max
Imaging arm	**men**	50.24	50	13.84	18	84
	women	46.45	45	10.73	15	70
Clinical arm	**men**	42.78	45	12.42	20	72

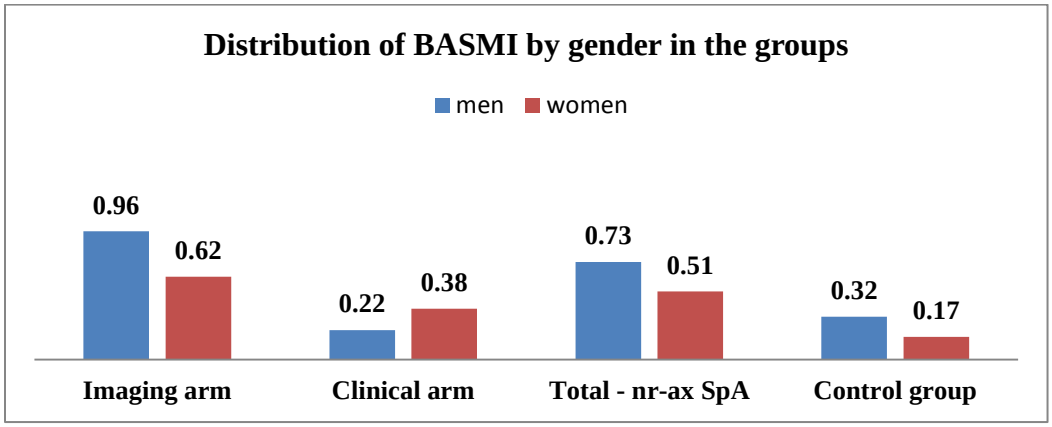
	women	40.15	40	12.96	20	67
nr-ax SpA total	**men**	47.92	49	13.77	18	84
	women	43.59	45	12.15	15	70
Control group	**men**	21.16	20	8.36	10	42
	women	18.22	18	5.91	8	30

V.3.3 Clinical assessment of the level of spinal impairment in nr-ax SpA (including intragroup in imaging and clinical arm) and control group by sex:

V.3.3.1 Bath Ankylosing Spondylitis Metrology Index –BASMI

The assessment of the level of spinal mobility using the ***BASMI*** composite index shows some differences between the two sexes. Despite the early diagnosis of Nr-ax SpA, the diagnosis in patients is a certain degree of axial structural changes associated with motor deficits. ***BASMI*** is highest in men with Nr-ax SpA-imaging arm (average 0.96). Figure 22 presents the results of ***BASMI*** for men and women in each group. The tendency for higher mean values of this indicator in men is disturbed only in the subgroup of patients with Nr-ax SpA - clinical arm, where the results are 0.22 ± 0.15 in men and 0.38 ± 0.6 in women. Men with MRI changes of the SIJ had a statistically significantly higher degree of axial damage according to ***BASMI*** in the analyzes in the subgroup of patients with the imaging arm - 0.96 ± 0.6 vs 0.62 ± 0.3 (***p <0.02***).

Figure 22: The mean values of the degree of spinal impairment, by ***BASMI*** in ***both sexes*** in all groups and subgroups are presented:



V.3.4 Assessment of changes in sacroiliac joints (SIJ) by magnetic resonance imaging (MRI) in men and women (SPARCC):

Both men and women from the imaging arm showed similar SPARCC values of 23.31 ± 14.62 and 21.4 ± 15.86, respectively (***p = 0.546***). Although there were no MRI changes of the SIJ in patients from the clinical arm, discrete ones were reported in single patients, which allowed to register SPARCC 0.26 ± 0.915 in men and 0.08 ± 0 in women with ***p <0.05***. The difference in SPARCC between the two sexes in the general group of patients with Nr-ax SpA ***(p <0.05)*** was also statistically significant.

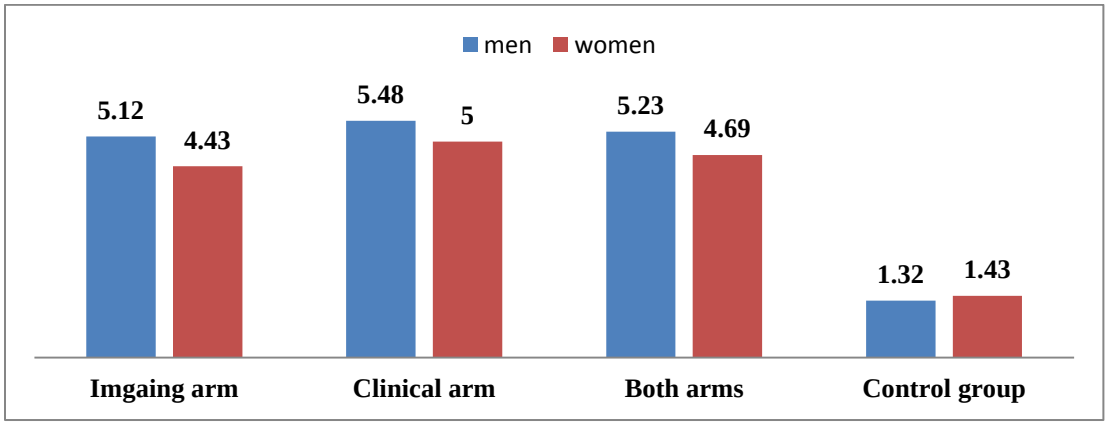
Table 32*:** Descriptive analysis of MRI changes in the SIS, presented by ***SPARCC in nr-ax SpA in the imaging and clinical arm, total Nr-ax SpA and the control group ***in both sexes***:

Patient group		SPARCC	Median	±SD	Min	Max	p
Imaging arm	**men**	**23.31**	19	14.62	4	60	p = 0.546
	women	**21.4**	18	15.86	2	63	
Clinical arm	**men**	**0.26**	0	0.915	0	4	**p<0.05**
	women	**0.08**	0	0.48	0	3	
nr-ax SpA total	**men**	**16.15**	11	16.19	0	60	**p<0.05**
	women	**11.73**	4	15.84	0	63	
Control group	**men**	**NA**	NA	NA	NA	NA	NA
	women	**NA**	NA	NA	NA	NA	

V.3.5 Assessment of quality of life using the disease-specific questionnaire Ankylosing Spondylitis Quality of Life (ASQoL) for nr-ax SpA (including subgroup in imaging and clinical arm) and the control group by sex:

The quality of life in both sexes of patients with Nr-ax SpA has deteriorated. The mean values of **ASQoL** in men and women with **Nr-ax SpA-imaging arm** were 5.23 ± 3.02 and 4.43 ± 2.13 (***p = 0.78***). Despite the higher mean values of the score assessing the quality of life in men with **Nr-ax SpA-clinical arm,** there is no statistically significant difference compared to women in the same subgroup - 5.48 ± 3.15 vs 5.0 ± 2.95 (***p = 0.68***). We found a deterioration in quality of life when comparing ASQoL in **Nr-ax SpA and the control group** for both sexes - ***p <0.05***.

Figure 23: The average change in the quality of life of the participants, measured by ***ASQoL*** in the individual groups by ***sex***, is presented:



In the **general group of patients with Nr-ax SpA,** there was no statistically significant difference in the change in quality of life, according to the results of the ASQoL score in men and women - 5.23 ± 3.450 vs 4.69 ± 2.92 (***p = 0.283***). (Table 33):

Table 33: Details of the analysis of the change in quality of life measured by ***ASQoL*** in ***men and women*** with Nr-ax SpA (N = 160):

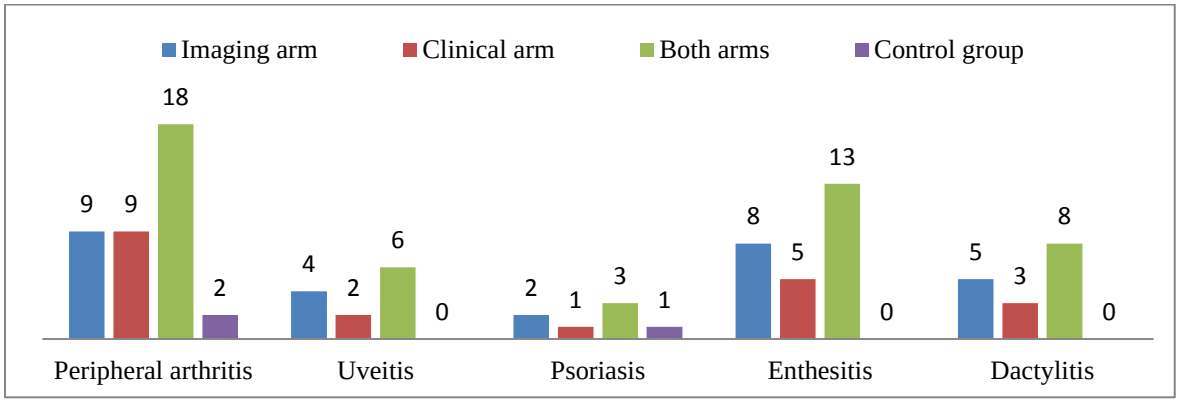
Group		N	Mean value	Standard deviation	Standard error	p
ASQoL	men	74	**5.23**	3.450	.401	**p= 0.283**
ASQoL	women	86	**4.69**	2.928	.316	

V.4 Assessment of the prevalence of extraaxial manifestations in patients with nr-ax SpA, incl. subgroup and by gender:

V.4.1 Distribution of extraaxial manifestations of nr-ax SpA among men in different groups:

The relative share of men in the **imaging arm** with peripheral joint symptoms is 18% (n = 9/50), and the percentage of dactylitis - 10% (n = 5/50). In 8% (n = 4/50) acute anterior uveitis was registered, in 16% (n = 8/50) - enthesitis and only in 4% (n = 2/50) of the men in the subgroup - cutaneous form of psoriasis. In the **clinical arm** of nr-ax SpA, men with peripheral arthritis were 39%, with dactylitis 13%, and with enthesitis, uveitis and psoriasis - 21.7%, 8.6% and 4.3%, respectively. Overall, in men with nr-ax SpA, the highest relative proportion of extraaxial manifestations was 24.6% with peripheral arthritis and 17.8% with enthesitis. The distribution by number of patients in the different groups is presented in ***Figure 24.***

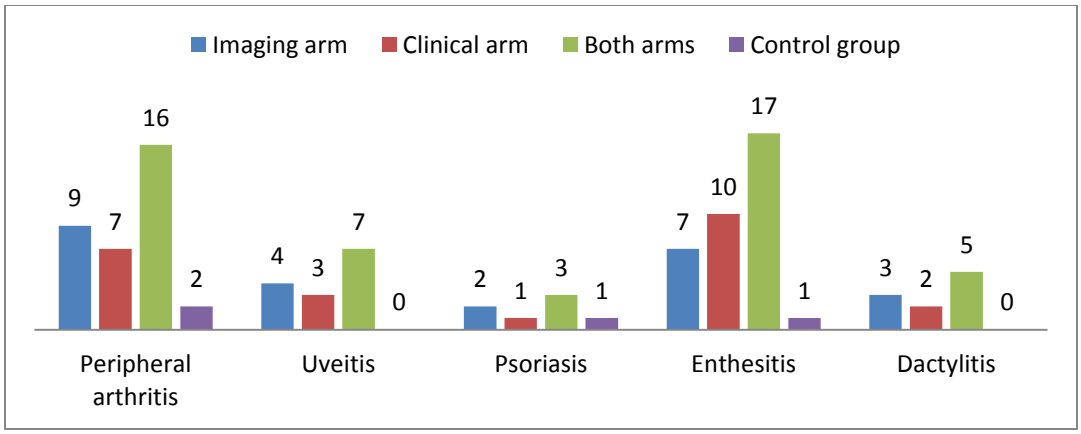
Figure 24: *The frequency of prevalence (number of men) of extraaxial symptoms in* ***men*** *in the considered groups and the control group is presented:*



V.4.2 *Prevalence of extraaxial manifestations of nr-ax SpA among* ***women*** *in different groups:*

The most common extraaxial manifestation in women with nr-ax SpA is **enthesitis** (19.5%), in 18.3% **peripheral arthritis** is registered, in 6.8% - **acute anterior uveitis**, in 9.2% - **dactylitis** and in 3.4% - **cutaneous plaque psoriasis**. The distribution of extravertebral symptoms in the individual subgroups in women is shown in ***Figure 25***.

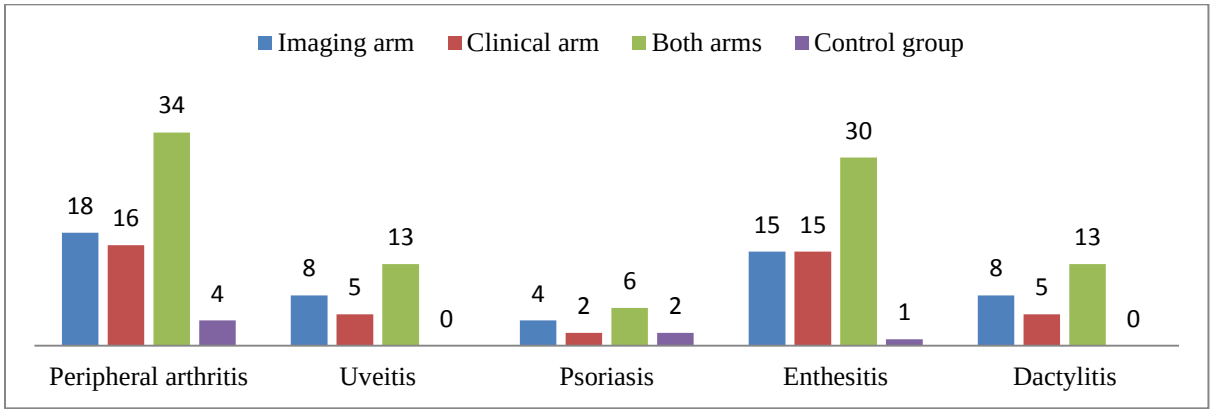
Figure 25: *Frequency of extraaxial symptoms (EAS) in women with Nr-ax SpA and control group (number of patients, N):*



V.4.3 The overall distribution of extraaxial manifestations among the study population and the control group:

The most common extravertebral manifestation in *patients with nr-ax SpA* is **peripheral arthritis** - in 21.5%. Its frequency is approximately similar for both sexes in patients from both the imaging and clinical arm. The relative share of patients with **dactylitis** in the group of nr-ax SpA is 8.1%, and with **enthesitis** we registered - 18.7%. Peripheral arthritis (9.5%), cutaneous psoriasis (4.7%) and enthesitis (2.3%) were registered in the control group, ***Figure 26***:

Figure 26: Frequency of EAS common to both sexes in the different groups and subgroups of participants in the study:

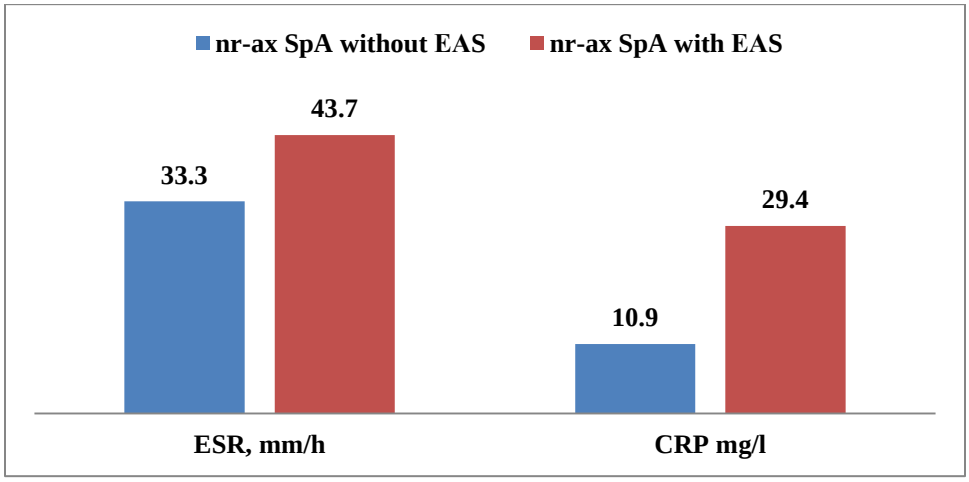


V.4.4 Comparative analyzes of patients with nr-ax SpA with and without extraaxial manifestations

In the following analyzes we will compare the studied laboratory parameters and clinical indices of disease activity in two groups of patients - patients with nr-ax SpA with isolated spinal disease and patients with nr-ax SpA with extraaxial symptoms (EAS). As EAS, only the two most common manifestations in the studied cohort will be included - peripheral arthritis and enthesitis. The mean ESR in patients with isolated spinal disease was 33.3 mm / h ± 9.87, compared to 43.7 mm / h ± 7.45 in patients with nr-ax SpA with peripheral arthritis or enthesitis. For the other acute phase protein, these values are 10.9 ± 4.6 and 29.4 ± 10.3, respectively

(***Figure 27***). Of the patients with nr-ax SpA without EAC, 37% had normal ESR values and 12.6% had normal CRP values. In the group of patients with nr-ax SpA with EAC, acute phase values were normal in 12.3% and 6.5% for ESR and CRP, respectively. The presented data show a higher laboratory activity of the disease, when there is evidence of peripheral arthritis or enthesitis in patients with nr-ax SpA.

Figure 27*: Mean values of acute-phase reactants in patients with nr-ax SpA with and without extraaxial symptoms:*



Data from the comparative analyzes of BASDAI, BASFI, ASDAS-CRP and ASQoL in patients with nr-ax SpA with or without peripheral arthritis / enthesitis are presented in Table 33. The mean values of the rates of disease activity BASDAI and BASFI in both groups are similar and there is no statistically significant difference. Mean ASDAS-CRP values were higher in the nr-ax SpA group with concomitant peripheral arthritis or enthesitis (***p <0.003***). The quality of life of both subgroups of patients was deteriorated with close mean values of ASQoL 5.44 (with EAC) and 5.01 (without EAC), ***p = 0.315***.

Table 34: Data from the comparative analyzes of the level of disease activity (via BASDAI and ASDAS-CRP), physical disability (BASFI) and the level of quality of life (ASQoL) in ***patients with Nr-ax SpA with or without EAS:***

Group		N=160	Mean value	Standard deviation	Standard error	p
BASDAI	+EAC	64	**4.48**	.7041	.0841	p= 0.218
BASDAI	-EAC	96	**4.01**	.6438	.0698	
BASFI	EAC	64	**5.13**	1.396	.144	p = 0.402
BASFI	-EAC	96	**4.56**	1.026	.112	
ASDAS – CRP	+ EAC	64	**3.351**	.9832	.1154	***p <0.003***
ASDAS – CRP	-EAC	96	**2.154**	.4872	.0613	
ASQoL	+EAC	64	**5.44**	3.599	.429	p =0.315
ASQoL	-EAC	96	**5.01**	3.128	.322	

Correlation dependence of acute phase indicators for laboratory and clinical indices of disease activity in patients with nr-ax SpA <u>with and without EAS</u>:

1. Nr-ax SpA with peripheral arthritis / enthesitis:

We found a weak correlation between ESR and CRP and BASDAI, ***respectively r = 0.2 and r = 0.27, p <0.05***. The correlation between CRP and ASDAS-CRP is moderate to significant, ***r = 0.46, p = 0.00***. The other indicators are shown in ***Table 35***:

Table 35: *Correlation matrix of dependence between API and indices for assessment of disease activity in* ***<u>Nr-ax SpA + EAC</u>****:*

		ESR	CRP
BASDAI	Correlation coefficient	.206**	.275**
	Sig.(2-tailed)	.002	.001
	N	64	64
ASDAS_CRP	Correlation coefficient	.395*	.462**
	Sig.(2-tailed)	.002	.000
	N	64	64
VAS patient	Correlation coefficient	.267*	.288*
	Sig.(2-tailed)	.032	.028
	N	64	64
VAS physician	Correlation coefficient	.260**	.289*
	Sig.(2-tailed)	.005	.012
	N	64	64

**.Statistically significant correlation at the level of 0.01.
* .Statistically significant correlation at level 0.05.

2. Nr-ax SpA without peripheral arthritis / enthesitis:

With the exception of ESR and BASDAI, which did not show correlation in the analysis, all other parameters have a statistically significant positive correlation with each other.

Table 36*: Correlation matrix of dependence between AFP and indices for assessment of disease activity in* ***Nr-ax SpA without EAS****:*

		ESR	CRP
BASDAI	Correlation coefficient		.315*
	Sig.(2-tailed)	n.s.	.035
	N	96	96
ASDAS_CRP	Correlation coefficient	.314*	.558**
	Sig.(2-tailed)	.042	.001
	N	96	96
VAS patitents	Correlation coefficient	.202*	.264*
	Sig.(2-tailed)	.003	.018

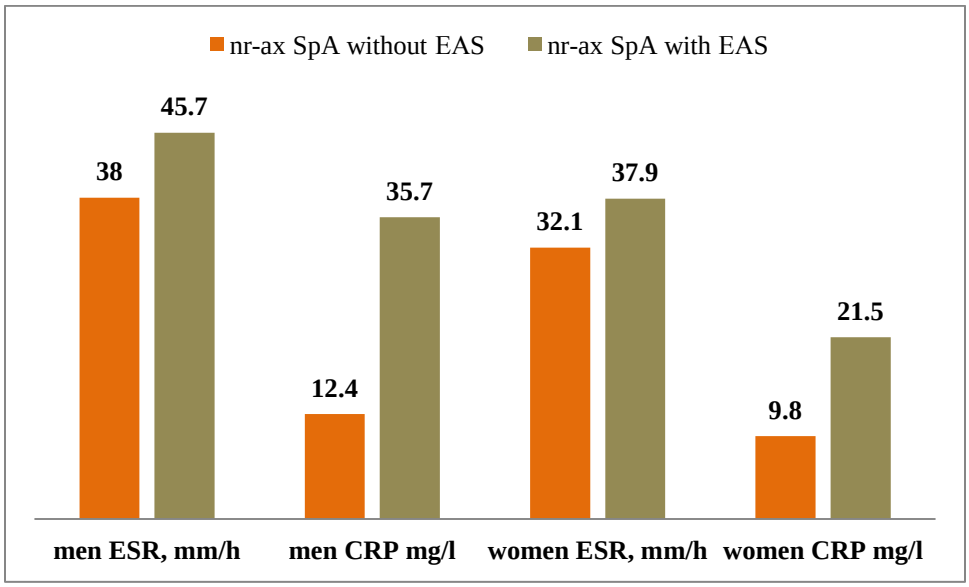
	N	96	96
VAS Physician	Correlation coefficient	.212*	.278*
	Sig.(2-tailed)	.002	.002
	N	96	96

**.Statistically significant correlation at the level of 0.01.
* .Statistically significant correlation at the level of 0.05.
n.s.-no statistical significance.

V.4.5 Comparative analyzes of patients with nr-ax SpA with and without extraaxial manifestations by sex

Higher CRP values were observed in both sexes, regardless of the absence and presence of extraaxial symptoms. Men with isolated spinal involvement had mean CRP values of 12.4 ± 5.4 versus 35.7 ± 11.2 in patients with peripheral arthritis or enthesitis (***p <0.05***). The difference between the mean CRP values in women with and without peripheral symptoms is also statistically significant. The erythrocyte sedimentation rate (ESR) in both sexes tended to be higher on average in the group of patients with peripheral arthritis or enthesitis, but the difference was not statistically significant (***p> 0.05***). Graphical visualization of the mean values of acute-phase reactants by sex in both groups of patients is presented in the following ***figure 28***:

Figure 28: *The mean values of* ***API*** *in* ***men and women*** *with* ***Nr-ax SpA with or without EAS*** *are presented:*



VI.5 Distribution of patients in different groups according to the treatment

Nr-axSpA is characterized by a short duration of symptoms and, in parallel, limited access to the ability to initiate a disease-modifying antirheumatic agent. Patients receiving anticytokine drugs (TNF alpha or IL-17a antagonists) were not included in the present study. At the time of the visit, all patients in the different groups were categorized into three areas according to the current treatment - patients not receiving treatment, those taking NSAIDs and patients with sulfasalazine.

The next three figures represent the relative share of patients in the three categories. Just over 50% of Nr-ax SpA-imaging arm patients on the date of the visit were taking NSAIDs. The relative proportion of patients with clinical Nr-ax SpA treatment with NSAIDs was 43%. The percentages of patients who did not and did not receive any treatment in the two subgroups were similar - 35.7% in the imaging arm and 39% in the clinical arm of Nr-ax SpA.

Given the recommendations for initiation of sulfasalazine in patients with peripheral synovitis, it is not surprising the higher relative proportion of patients from the clinical arm who reported taking this drug - 18%, compared to 13.2% in patients from the imaging arm. Similar are the relative proportions of patients who, despite the symptoms of the disease, were without treatment (35.7% in imaging and 39% in clinical arm).

***Figure 29**: Relative share of Nr-ax SpA patients in the three categories according to the treatment:*

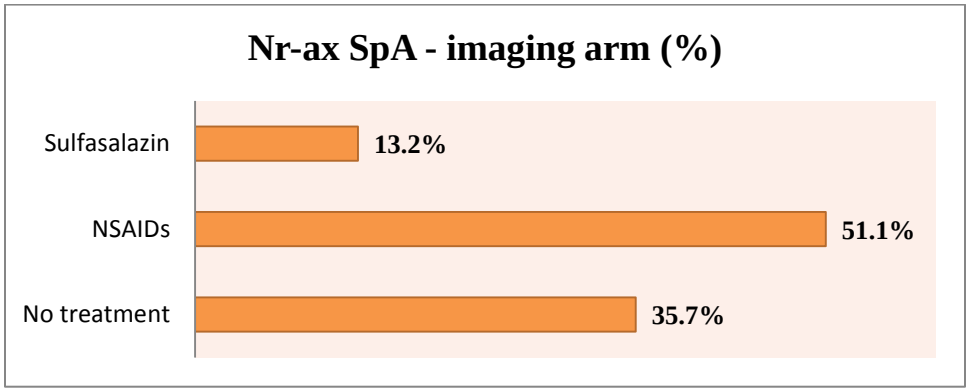


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***Figure 30**: Percentage distribution according to the conducted treatment in the group of patients from the clinical arm:*

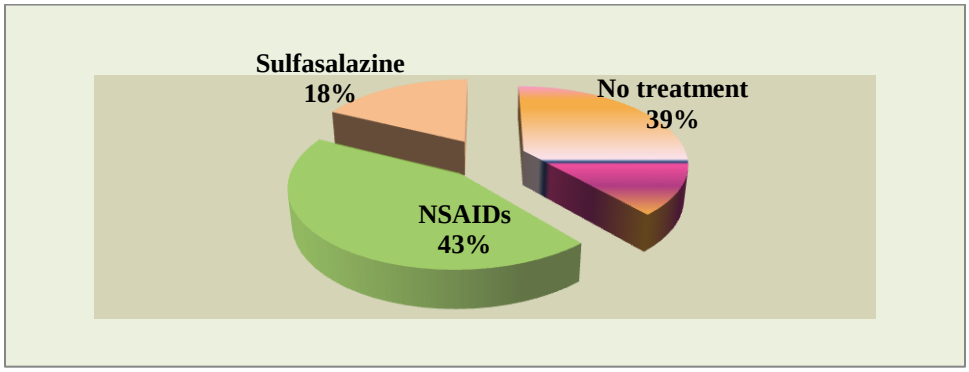
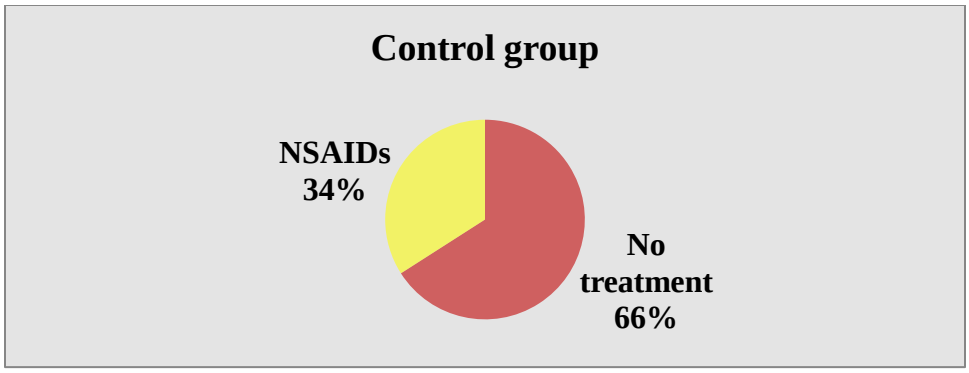
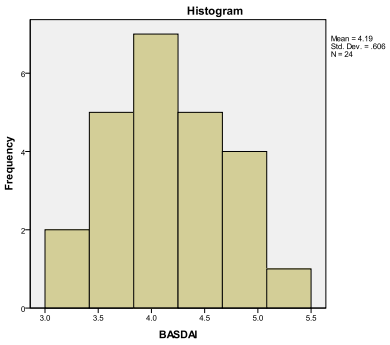


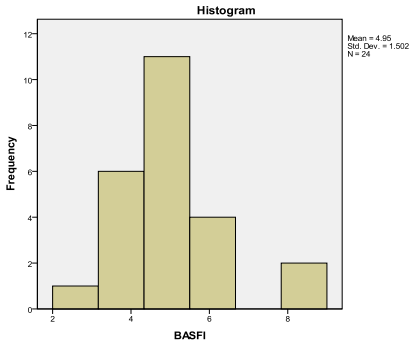
***Figure 31**: Distribution by relative share of patients according to the conducted treatment in the control group:*



In the control group, 66% had no treatment reports and only 34% reported NSAIDs. There were no sulasalazine-treated patients in this group.

We analyzed the effect of the two main groups of drugs used in patients with Nr-ax SpA and some of the clinical indices for assessing disease activity (BASDAI, BASFI and ASDAS-CRP). We performed the analysis in the sample distribution with a volume of 24 (a total of 24 patients receiving sulfasalazine), and only in **BASDAI and BASFI** the distributions can be approximated to normal and the data can be used to test statistical hypotheses.





The results of the analysis are summarized in the following ***table 37*** and show that in both groups of patients receiving NSAIDs and sulfasalazine have similar levels of disease activity degree of functional impairment, calculated by BASDAI and BASFI, respectively.

Table 37: *The data from the comparative analyzes for determining the influence of the* ***conducted treatment*** *on the index for assessment of disease activity (****BASDAI****) and score for functional assessment (****BASFI****) are presented:*

Group		N	Mean value	Standard deviation	Standard error	p
BASDAI	NSAIDs	77	**4.088**	.7798	.0889	**p= 0.553**
BASDAI	Sulfazalazine	24	**4.192**	.6057	.1236	
BASFI	NSAIDs	77	**4.83**	1.311	.149	**p= 0.699**
BASFI	Sulfazalazine	24	**4.95**	1.502	.307	

VI. DISCUSSION

Despite the change in the direction of diagnostic thinking in recent years from classic ankylosing spondylitis to its early form, there are still many cases of late diagnosis. In the context of the available possibilities for therapeutic modulation of the symptoms of the disease and slowing down its progression, the wide diagnostic thinking and the efforts made for the early detection of spondyloarthritis are justified - even in its non-radiographic phase. Good awareness of the disease, examination of patients in the target group and their timely referral to a rheumatologist are the basis of diagnostic success in the early stages of the disease (*Rudwaleit et al., 2012).* Initiation of treatment with different non-pharmacological and pharmacological groups of drugs plays an important role in improving the disease activity, physical function and quality of life of patients who are almost always between the ages of 18 and 45.

This was the main reason why the main aspects of non-radiological axial spondyloarthritis were considered in the present study - its laboratory and clinical disease activity, function, degree of spinal cord injury, MRI changes of SIJs and quality of life.

A number of scientific studies in the literature have shown similar overall levels of disease activity between nr-ax SpA and ankylosing spondylitis, indicating that the early phase is not "more sparing". And although the difficulty in performing daily activities in nr-ax SpA is largely related to the inflammatory aspects of the disease (rather than permanent structural changes), their quality of life is poor.

The age of the joint symptoms is extremely important for the diagnosis of the non-radiographic phase of the disease. In separate publications of Poddubnyy D et al. the duration of inflammatory spinal pain and the already existing structural changes in SpA are analyzed. *(Poddubnyy D et al., 2011, Poddubnyy D et al., 2018).* Identical in terms of age of inflammatory spinal pain (IBP) with our study is the DESIR study conducted in 475 patients in France. Of all patients selected for IBP for 3 months but less than 3 years, 62% were diagnosed with nr-ax SpA and 38% with ankylosing spondylitis *(Rudwaleit et al., 2009).* Precisely because of the focused diagnostic thinking in the direction of nr-ax SpA, we adopted an upper limit on the duration of the disease - 3 years. The SPACE study improved this result by including 60 patients with chronic spinal pain up to 2 years and finding 80% of patients with nr-ax SpA (van der Berg et al., 2012). The influence of the duration of symptoms on the occurrence of structural changes can be established on the basis of scientific projects that include patients with IBP with a longer history. The international study RADAR (397 patients) and MASTER in Germany (224 patients) have the largest number of patients included. Both studies included patients with chronic spinal pain and signs of spondyloarthritis more than 7 years old, with a relative proportion of patients with nr-ax SpA being 23% with RADAR and 38% with MASTER. The remaining participants (77% and 62%) meet the modified New York AU criteria *(Poddubnyy et al. 2011, Sieper et al., 2012).* Two studies of biological drugs with TNF alpha blocking have shown the same trend. The first included patients with a history of axial pain and stiffness less than 3 years, and found that 88% of them had pre-radiological disease *(Barkham et al., 2009).* In the second study, the duration of symptoms was less than 5 years, but already the relative proportion of patients with nr-ax SpA is 49% *(Song et al., 2011).*

These data from the medical literature, based on our results, give us reason to believe that we have established this age of symptoms at which nr-ax SpA is most likely to be diagnosed. The mean duration of symptoms in our study for the general group of patients with nr-ax SpA

was 7.4 months or 0.764 ± 0.27 years for the imaging arm and 0.487 ± 0.23 for the clinical arm. Despite the higher average duration of back pain in patients in the control group 1.17 ± 0.33 years, it is well below 3 years, which we consider a threshold above which the chance of already existing structural changes is greater.

The advent of the term radiographic phase of spondylitis has greatly changed the classical notion of gender distribution in the disease. For decades, ankylosing spondylitis has been thought to affect mostly men. In past publications, the male to female ratio of ankylosing spondylitis has been defined as 10: 1 *(West et al., 1949; Moll et al., 1974).* About 40 years ago, a Swiss study found a male-female ratio of 2.57 to 1 in patients with AC / ax SpA, and in 2016, this ratio was adjusted to 1.03 to 1 *(Baumberger et al., 2017).* Approximately the same sex ratio has been reported in a number of studies in patients with nr-ax SpA *(Rudwaleit et al., 2009; van der Berg et al., 2012; Sieper et al., 2013).* In the present scientific work, we found a ratio of nr-ax SpA between men and women - 1: 1.19. In the figurative arm this ratio is 1.04: 1, and in the clinical arm the female gender prevailed - 1: 1.6.

For the past 12 years, the HLA B27 antigen carrier has been recommended by the ASAS group as one of the main criteria for classifying patients with spondyloarthritis (Kitz et al., 2012; Kiltz et al. 2012). Its presence in combination with two or more features of the disease allows the diagnosis of SpA to be accepted, and on this basis it became possible to differentiate the clinical arm for the disease (ASAS classification criteria for axial spondyloarthritis). There is also a tendency for a lower percentage of HLA B27 antigenic carrier in nr-ax SpA compared to AC. We also found this in our results in the individual subgroups of nr-ax SpA. In a study by Weisman MH, the prevalence of HLA B27 after patients with nr-ax SpA was 86.4%, and in AC - 89.1% *(Weisman et al., 2013).* In another study by Braun A., this frequency was even lower - 74.8% for nr-ax SpA and 81.5% for AC (respectively, Braun et al., 2011). In the study population, 90.3% of the whole group of patients with nr-ax SpA (80.6% in nr-ax SpA - shaped arm) had HLA B27 antigenic carrier.

❖ Evaluation of disease activity in nr-ax SpA

The level of disease activity in patients with nr-ax SpA is the subject of increased attention by leading global experts in the field of spondyloarthritis, as well as pharmaceutical companies whose drugs affect it. Evidence of similar levels of disease activity in the early pre-radiological and later radiographic phases of SpA has led the lens to a detailed study and to determine the possibilities for early therapeutic initiation and impact. In nr-ax SpA, lower values of laboratory markers of inflammation are observed in cases of discrete or absent inflammatory changes of MRI in the SIJs and spine. Despite these features, the two phases of SpA report similar parameters in terms of disease activity, physical function, and impaired quality of life *(Boonen et al., 2015).*

❖ Inflammatory biomarkers

A number of studies have found that serum CRP levels and ESR values are not always high in nr-ax SpA. This is a well-known fact in patients with AC, where approximately 40% have normal acute phase reactants. The possibility of registering CRP in reference values is a bit

confusing, given that its high value is one of the characteristics of spondyloarthritis in the classification criteria of ASAS experts from 2010. Their study in routine clinical practice should remain mandatory in cases of a patient with an inflammatory type of spinal pain when SpA is suspected. In cases of spondyloarthritis with peripheral joint symptoms, the values of these biomarkers are almost always high (Turina et al., 2017). In the present study, the group of patients with nr-ax SpA had mean ESR values of 37.35 ± 14.6 mm / h and a CRP of 10.93 ± 6.2. In the figurative arm, 10.2% had normal ESR values and 31.63% had CRPs below 5 mg / L. In the clinical arm, the relative share of normal acute-phase parameters is higher - 27.4% for ESR and 45.1% for CRP, respectively. These values as a trend largely correspond to the data reported in the medical literature by other authors. It is important to note that biomarkers of inflammation are higher in patients who have MRI data for bone marrow edema.

❖ Clinical indices for disease activity

In the present scientific study, we used the established activity rates not only in everyday practice, but also in large clinical trials. They are all validated in spondyloarthritis. With the exception of the ASDAS score, the other included indicators that we used are entirely subjective and are based solely on information provided by the patient.

The most widely used is the Bath Ankylosing Spondylits Disease Activity Score (BASDAI). Although there is debate about determining the value above which high disease activity is assumed, it is accepted that it is 4. BASDAI≥4 in combination with the expert opinion of the attending physician is often enough to re-evaluate the patient's treatment plan. It consists of 6 questions, four of which relate to pain and fatigue in individual joint areas, while for the other two questions, patients provide information on the presence and duration of morning stiffness *(Landewe et al., 2015*). The other newer indicator of disease activity, ASDAS-CRP, includes, in addition to subjective patient data, pain, stiffness, peripheral joint pain, general assessment of the disease, and CRP value. This makes ASDAS-CRP a more preferred index of disease activity. In most cases, ASDAS values, not BASDAI values, are taken into account when deciding on a change in treatment plan. In studies by Marona J. and co-authors from 2020. ASDAS is favored when biological therapy is included and ASDAS> 2.1 is accepted as a criterion for this *(Marona et al., 2015).* The results in our patients with respect to BASDAI show that its mean values for nr-ax SpA exceed the threshold of 4. We found even higher BASDAI in patients with bone marrow edema of the SIS. We did not register a statistically significant difference between BASDAI in the two subgroups, and in the whole group of patients with nr-ax SpA, this indicator on average indicates a high degree of disease activity.

A study by Spoorenberg A. et al focuses on less and less single-component measurements (VAS) *(Spoorenberg et al., 2005).* In our study, we used a visual analog scale (0-10 cm) according to the patient and the doctor. The disease activity was assessed as high in VAS> 6 cm, inactive disease below 4. It was found that in a similar assessment of the total disease activity, the patient's assessment is higher than that of the attending physician. There are a number of factors for this, such as focusing on the degree of pain, stiffness, impaired physical function (by the patient) and focusing on some objective data on disease activity - CRP, ESR, imaging (by the doctor) . Despite the analyzed differences, the two indices of disease activity (VAS according to the patient and VAS according to the doctor) have a high degree of positive correlation, as shown in our results and should be supplemented when performing analyzes.

❖ Functional assessment of patients with nr-ax SpA

Functional assessment is extremely important in the overall assessment of disease activity and is in an intermediate position between clinically defined disease activity and the degree of manifestation of structural changes. In our study, we used the Bath Ankylosing Spondylitis Functional Index, designed to assess the functional status of patients with ankylosing spondylitis more than 20 years ago. BASFI is composed of 10 questions, each of which is based on the method of one-component analysis (0-10 cm). This questionnaire is addressed to patients with SpA, raising questions about the results of BASFI when used in a healthy population. Age-related common structural changes could affect the outcome of BASFI *(Wariaghli et al., 2012).* This is projected in our BASFI results in the control group - all 42 patients with non-inflammatory spinal pain were defined as BASFI <4. The extensive GESPIC study in 210 patients with early ax SpA demonstrated the association between disease activity and functional status of the patient, as well as MRI-detected inflammation and changes in functional status (Machado et al., 2010; Poddubnyy et al., 2018). In the same study, BASFI values between AC and early ax SpA were similar. The highest response rates in the patients we studied were the following statements: "Put on your socks or tights without help or aid (ie sock shoe)" and "Lean forward from the waist to pick up from the floor a chemical without an aid '.

- **Assessment of axial mobility**

Following the description of the BASMI composite index by Jenkinson T., it has emerged as a relatively short-term and reliable method for assessing the degree of spinal cord injury *(Jenkinson et al., 1994).* BASMI is based on 5 standard clinical measurements that most accurately reflect axial status: cervical rotation, tragus wall distance, lateral flexion, modified Schober test, and intermaleolar distance. In a study by *Hebeisen M. et al.,* the authors demonstrated a statistically significant difference between the degree of spinal cord injury between patients with nr-ax SpA and r-ax SpA (1.3 vs 2.5, p <0.001) *(Hebeisen et al., 2020).* These data are confirmed by our analysis from 2019, again in a comparative analysis of the two groups of patients *(Ivanova et al., 2018).* The results obtained in patients with nr-ax SpA confirm the data on low degree of spinal cord injury in the early phase of the disease. The mean BASMI value for the whole group is less than 1, being higher in the imaging arm group. This proves once again the claim that patients with changes in imaging (including magnetic resonance imaging) have more pronounced motor limitations.

- **QoL in Nr – ax SpA**

Spondyloarthritis affects all aspects of quality of life, incl. career development and sports selection *(Rosenbaum et al., 2019).* Prolonged disease activity has the greatest impact on patients' daily activities. Moreover, the presence of extraaxial and extraarticular manifestations (psoriasis, inflammatory bowel disease, etc.), as well as adverse events related to therapy and comorbidity, contribute negatively to the level of quality of life *(Kang et al., 2010, Shen et al., 2016).* Strategies and recommendations for the treatment of SpA have the task of reducing levels of disease activity and slowing radiographic progression in patients, but also greatly improve the quality of life of patients in all its dimensions *(van der Heijde et al., 2017*). The ASQoL Quality of Life Assessment Questionnaire used in this research is aimed at patients with spondyloarthritis and can be used at any stage. One reason for this is that ASQoL is not affected by whether patients are in the pre-radiological stage or have registered structural changes. In a study by *Doward L.,* ASQoL showed a strong positive correlation with various aspects of other scales

used to assess quality of life, such as NHP (Nottingam Health Profile), BASFI, LDQ (Leeds Disability Questionnaire and DFI (Dougados Funcional Index) (*Rosenbaum et al., 2019*). Приложението на биологични средства при болните от nr-ax SpA не е асоциирано с влошаване на качеството на живот *(Rohde et al., 2020).* This once again reveals the need for early diagnosis and the possibility of timely initiation of specific treatment. The most common positive responses in our study in the nr-ax SpA group were *"I can't sleep"* and *"I'm tired all the time"* in both sexes. For women, we found frequent positive responses in *"I'm Worried to Disappoint People"* and *"Pain is Always There."* This suggests a certain dominance of the psycho-emotional aspect, such as participation in the formation of quality of life in women with nr-ax SpA.

MRI changes of SIJs

The classic view of the absence of ankylosing spondylitis without radiographic evidence of sacroiliitis remains valid today. The implementation of the ASAS classification criteria for spondyloarthritis has greatly expanded the spectrum of the disease. Key points in these criteria are the inclusion of MRI changes compatible with SpA, the possibility of including all characteristics of SpA, as well as the positioning of HLA B27 antigenic carrier among the main criteria. All of them "displaced" the classic radiographic sacroiliitis in the background and paved the way for adequate early diagnosis. Moreover, only on the basis of HLA B27 antigenic carrier and more than two SpA characteristics, it became possible to accept the diagnosis nr-ax SpA - clinical arm.

However, sacroiliac joints remain the focus of attention, even with imaging techniques with the possibility of good resolution, such as MRI. MRI also has the leading advantage of certifying the presence of acute inflammatory lesions - synovitis, capsulitis, enthesitis and bone marrow edema, which is another advantage over conventional radiography and computed tomography. In theoretical terms, MRI acute changes can be monitored in dynamics, in order to assess therapeutic success, although this is not a daily practice. Disadvantages of the study, in addition to the high cost and lack of access to research in some regions, is the need for MRI examination in several areas. In large multicenter studies, the suspicion of spondyloarthritis necessitates MRI according to a protocol that includes the spine and SIJs.After carefully analyzing the different scoring systems for assessing changes in MRI in various scientific studies, the SPARCC score finds the greatest application. According to the ASAS / OMERACT MRI Working Group at SpA and in a study by *Truong SL et al. from 2021*, SPARCC is a relatively easy and fast method to retrieve, with reproducibility (*Truong et al., 2021*). In a study by *Rusman T. et al from 2019*, patients with nr-ax SpA and a high degree of activity were followed for a period of 6 months. They prove that inflammatory spinal pain with a high degree of activity is a prerequisite for the presence of bone marrow edema in the SIS or spine. According to this study, these changes are more common in men with IBP than in women. Another interesting fact is that patients with negative MRI remain so in over 95% of cases up to 6 months, despite persistently high levels of disease activity (*Rusman et al., 2020).*

VI.1 Opportunities for future additions to the present work

The current research can be considered as a basis for further prospective analyzes. Future analyzes that would be important in patients with nr-ax SpA can be considered in several ways:

1. To estimate in the future how many of the patients with nr-ax SpA pass into the phase with structural changes (AS) and how many of them remain in the non-radiographic phase and for how long. What is the probability of progression?

2. How many of the patients in the clinical arm after a certain period of time already have MRI inflammatory changes, ie. pass into the subset of the figurative arm. What is the probability of "conversion"? How does the quality of life of patients change when moving from one group to another?

3. To assess the dynamics of MRI inflammatory changes, to assess whether there is a possibility of "self-abatement" of the disease.

4. How do biological agents already registered in practice for the treatment of nr-ax SpA affect the disease activity, the degree of progression and the possibilities for permanent remission for the disease?

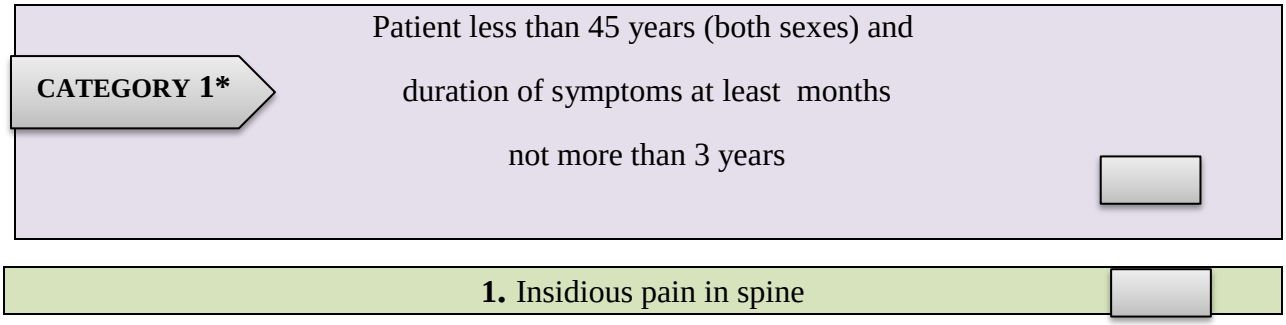
VI.2 Algorithm proposal

in the diagnosis of non-radiographic axial spondyloarthritis

in daily clinical practice

It is extremely important at the moment to optimize the possibilities for early diagnosis. The lack of irreversible structural changes in the axial skeleton and peripheral joints is the basis of the possibility of normal functioning of patients in cases of controlled disease activity. This undoubtedly **affects their quality of life in its various aspects**. These are the reasons why we have developed a simplified algorithm for work, which applied in clinical practice, we believe would improve the possibilities for early diagnosis. It is based on the latest ASAS classification criteria for spondyloarthritis (Annex № 10) and the ASAS criteria for inflammatory spinal pain (Annex № 12-III). It differs in that it is targeted at patients with non-radiographic axial spondyloarthritis, includes indices for assessing disease activity, and has guidance for monitoring and future reassessment of the condition.

The algorithm we offer **after an in-depth analysis of the medical literature and our personal results** includes 8 categories. They affect various aspects of the disease - demographics, age, initial clinical symptoms, genetic and laboratory markers, imaging studies and results, as well as the degree of disease activity**.**



2. Nocturnal pain (worst after waking in the morning)

CATEGORY 2**

3. Onset of symptoms before 45 years.

4. Improvement after physical activity

5. Worsening at rest.

CATEGORY 3*

- **Absense** of radiographic sacroiliitis I-IV grade on X-ray or CT
- **Absence** of structural changes in spine on X-ray or CT.

CATEGORY 4* **HLA B27 antigen (+)/(-)**

CATEGORY 5* **Elevated ESR and/or CRP**

CATEGORY 6*

MRI data for BME +/- synovitis, capsulitis or enthesitis of SIJs and/or spine

Presence of extraaxial and extraarticular manifestations:

CATEGORY 7*

- Peripheral mono-/ oligoarthritis
- Enthesitis
- Dactyitis
- Uveitis

CATEGORY 8***

BASDAI ≥4

and / or

ASDAS-CRP ≥2.1

Legend:

*** Categories 1, 2 and 3 are mandatory.**

****** Presence of at least 4/5 ASAS criteria for inflammatory spinal pain *(Sieper J., et al., 2009)*

******* Optional categories, but each implemented category (or part of it) increases the likelihood of nr-ax SpA.

The presence of categories 1 + 2 + 3+ 4 is sufficient to direct the clinician's attention towards **the clinical arm of nr-ax SpA**. The addition of categories 5 and / or 6 significantly increases the likelihood of **nr-ax SpA-imaging arm**. Category 7 has a guiding character in the direction of SpA and a positive response to one of its domains will support not only diagnostic thinking, but also the presumed level of disease activity. Category 8 is entirely focused on defining disease activity and is confirmatory.

The lack of confirmation in categories 5 and / or 6, but persistent positive characteristics in categories 2, 7 and 8, require time tracking and reassessment after 3 months for category 5 and 6 months for category 6.

The algorithm proposed for convenience in everyday clinical practice is yet to prove its capabilities and advantages in the direction of early diagnosis of SpA, and could undergo adjustments and updates according to the results of its application.

VII. CONCLUSIONS

1. We found a positive correlation between laboratory biomarkers of inflammation and clinical indices for disease assessment and functional impairment in patients with Nr-ax SpA.
2. Changes in magnetic resonance imaging of the sacroiliac joints show a strong positive correlation with markers of inflammation and scores for assessing disease activity in patients with nr-ax SpA.
3. Non-radiographic axial spondyloarthritis affects physical function. Functional impairment is higher in patients with extravertebral symptoms - peripheral arthritis or enthesitis.
4. Changes in spinal motility in nr-ax SpA are significantly more pronounced compared to the control group. The nr-ax SpA imaging arm showed a statistically significantly higher degree of axial damage than the clinical arm.
5. The quality of life of patients with nr-ax SpA is lower than in the control group of patients. It correlates positively with laboratory biomarkers for inflammation and indices for assessing disease activity. We did not find a significant difference between the level of quality of life in patients with imaging and clinical arm of nr-ax SpA.
6. We found statistically significantly higher values of OFP and ASDAS-CRP in men with Nr-ax SpA compared to women. There are no significant differences in the assessment of physical function, quality of life and SPARCC between the sexes.
7. Treatment with NSAIDs and sulfasalazine did not affect disease activity (BASDAI) and physical function (BASFI) in patients with Nr-ax SpA.

8. We found the negative impact of smoking on quality of life (ASQoL) in patients with Nr-ax SpA.

VIII. Contributions

VIII.1 Contributions of a original nature:

1. For the first time in Bulgaria patients with non-radiographic axial spondyloarthritis are examined and analyzed - their demographic characteristics, assessment of laboratory and disease activity, physical function, motor deficit and quality of life.

2. For the first time in Bulgaria and one of the few studies in the world that compares the image and clinical shoulder of patients with non-radiographic axial spondyloarthritis.

3. For the first time in Bulgaria and one of the few studies in the world that compares the two sexes not only in the general group of patients with nr-ax SpA, but also in subgroups.

4. For the first time in Bulgaria the connection of the SPARCC scoring system with the level of general disease activity and quality of life in patients with nr-ax SpA is established.

5. For the first time, a simplified algorithm has been proposed to help the rheumatologist's daily clinical practice, which aims to optimize the possibilities for early diagnosis of SpA in the non-radiographic phase.

VIII.2 Contributions of a confirmatory nature:

1. It is confirmed that despite the absence of irreversible structural changes and a short duration of symptoms in nr-ax SpA, the quality of life deteriorates.

2. Approximately the same sexual performance in nr-ax SpA was confirmed, as well as the association of males with higher levels of disease activity.

3. The connection between the acute phase indicators and the level of assessment of the disease activity is confirmed.

4. Higher levels of disease activity according to ASDAS-CRP in patients with extraaxial manifestations have been confirmed.

5. The link between smoking and deteriorating quality of life, as measured by ASQoL, in patients with nr-ax SpA was confirmed.

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